HETEROCYCLE STABILIZED CARBANIONS: NOVEL SYNTHON EQUIVALENTS IN ORGANIC SYNTHESIS

BY

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To my wife, Xiaohong

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Abstract of Dissertation Presented to the Graduate School of the University of Florida in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

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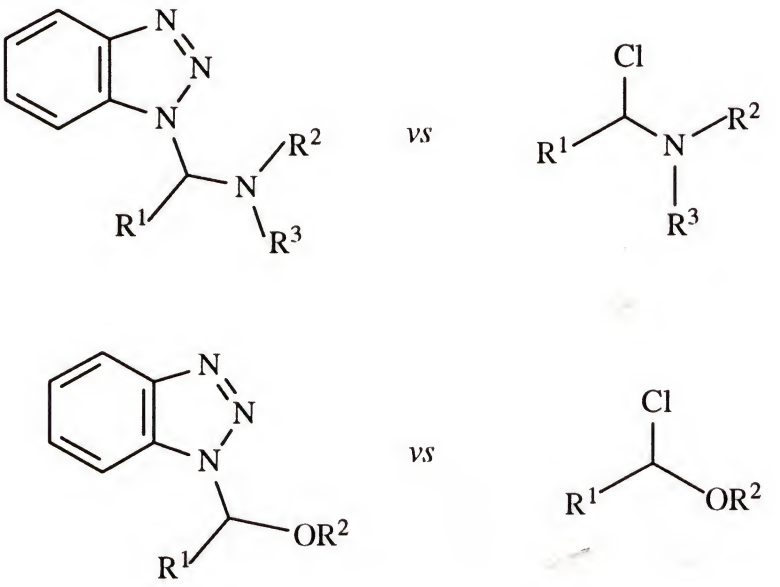
Chairman: Alan R. Katritzky, FRS
Major Department: Chemistry

Benzotriazole-activated methane systems readily undergo lithiation and reaction with electrophiles to afford the corresponding adducts, which, upon acidic hydrolysis, give the corresponding α-functionalized aldehydes, formylsilanes, ketones and carboxylic acids. Thus, tris(benzotriazol-1-yl)methyl anion reacts with alkyl halides, acyl chlorides, aldehydes and isothiocyanates to give the corresponding intermediate products which are then hydrolyzed in the presence of sulfuric acid to afford the corresponding α-functionalized carboxylic acids. In this way, tris(benzotriazol-1-yl)methyl anion functions as a novel carboxyl anion equivalent. Following a similar protocol, (benzotriazol-1-yl)(carbazol-9-yl)methyl anion functions as a formyl anion equivalent utilized for the synthesis of a wide variety of α-functionalized aldehydes. This system has been successfully extended to the synthesis of formylsilanes which have been long regarded as unstable species. Substituted (benzotriazol-1-yl)(carbazol-9-yl)methanes can undergo further lithiation and subsequent reaction with electrophiles to give the disubstituted products which are then hydrolyzed to afford the corresponding ketones. When a dialkylaminoethyl group is used as the substituent, such a system functions as a novel β-aminoacyl synthon equivalent.

(Benzotriazol-1-yl)phenylthiomethane has been shown to be a useful 1,1-dipole synthon equivalent in aromatic annulations. Thus treatment of (benzotriazol-1-yl)phenylthiomethane with butyllithium followed by quenching with appropriate alkyl halides provides the requisite intermediates which then undergo Lewis acid-catalyzed cyclization to afford the corresponding annulated products.

CHAPTER I
GENERAL INTRODUCTION

In recent years, the use of benzotriazole as a synthetic auxiliary has been extensively investigated in this research group [91T2863]. One of the special features attributing to the usefulness of benzotriazole is its acidity ($pK_a \approx 8$) which gives it two important properties. One is that it readily undergoes Mannich-type reactions with aldehydes and amines, amides, alcohols, or thiols to form the corresponding condensation products, and the other is that its anion is a good leaving group which can be displaced by various types of nucleophiles, such as Grignard reagents, hydride, enolate ions, alkoxides, thiolates, *etc.* This combination allows a wide variety of

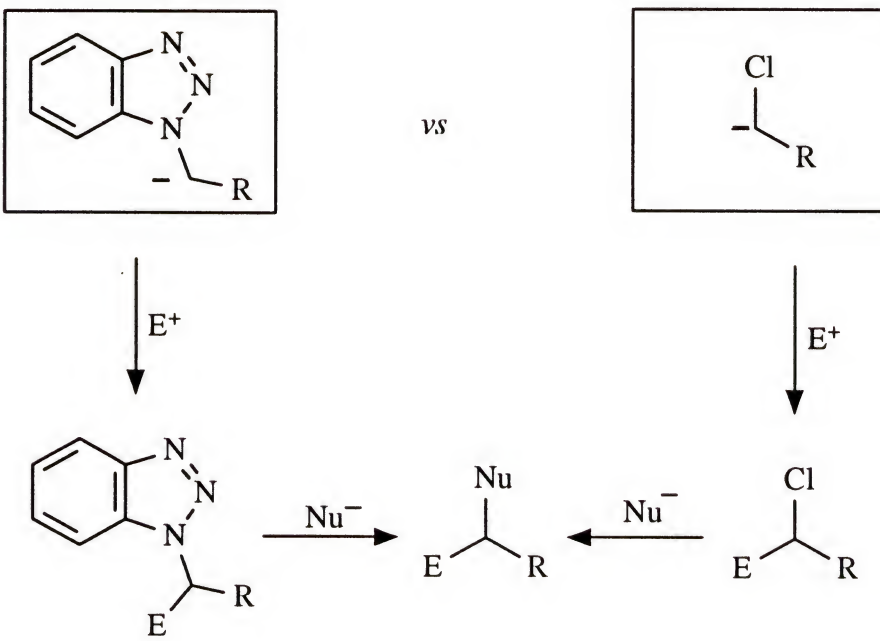


1.1 Benzotriazole - An Advantageous Tame Halogen Substitute

organic compounds to be readily accessible, such as primary, secondary and tertiary amines, amides, enamines, ethers, vinylethers, thioethers, etc. Since α-chloroalkyl amines and α-chloroalkyl ethers are in general highly unstable and physiologically

hazardous, the benzotriazole-mediated methodology not only provides an alternative approach to the compounds described above, but also proves to be a highly advantageous one and in some cases even a necessity.

Obviously, the utilization of benzotriazole as a synthetic auxiliary has by no means been limited to the above areas. The strong electron-withdrawing ability of benzotriazole increases the richness of its chemistry as it can sufficiently stabilize α-carbanions. This property, together with the well-established leaving ability of



R : CH_3, Et, Ph, allyl, OMe, SR, heterocycles, etc

1.2 Benzotriazole - An Advantageous α-Carbanion Stabilizing Moiety

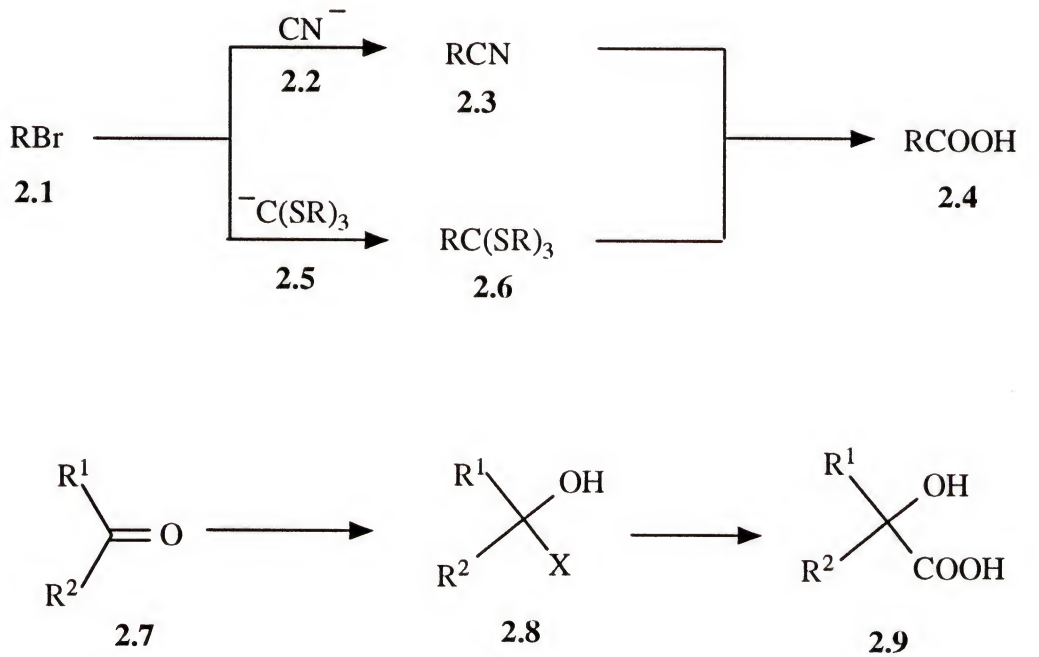
benzotriazolate anion as mentioned above, greatly extends the applications of benzotriazole in organic synthesis. The advantage of benzotriazole-mediated methodology is even more obvious here if one considers the fact that a carbanion stabilized by an α-chlorine or other halogen atom is generally unstable.

It is the objective of this project to investigate the possibilities of benzotriazole stabilized carbanions to function as useful anion synthon equivalents, and this will be examined in six chapters. Chapter II deals with the utilization of tris(benzotriazol-1-yl)methane as a carboxyl anion synthon equivalent. Thus, lithiation of tris(benzotriazol-1-yl)methane and subsequent reaction with electrophiles gives the corresponding intermediate products which are hydrolyzed under acidic conditions to produce the respective carboxylic acids with one carbon elongation. Chapters III and IV describe the use of (benzotriazol-1-yl)(carbazol-9-yl)methane as a formyl synthon equivalent based on a similar protocol leading to the synthesis of α-functionalized aldehydes and formylsilanes. The work discussed in Chapters V and VI extends the benzotriazole-carbazole-stabilized anion system to the synthesis of α-functionalized ketones and β-aminoethyl ketones using substituted (benzotriazol-1-yl)(carbazol-9-yl)methanes as acyl synthon equivalents. Chapter VII demonstrates the utility of (benzotriazol-1-yl)phenylthiomethane to function as a 1,1-dipole synthon equivalent in aromatic annulations.

CHAPTER II
TRIS(BENZOTRIAZOL-1-YL)METHANE: A NOVEL CARBOXYL SYNTHON EQUIVALENT

2.1 Introduction

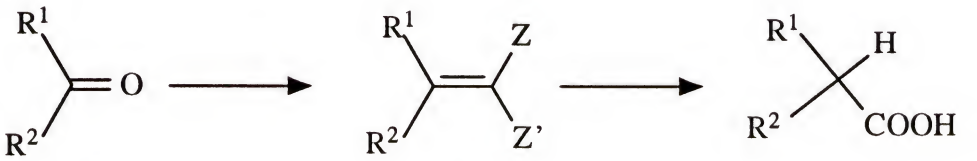
The synthesis of carboxylic acids by one-carbon homologation has relied on a variety of masked carboxyl anion equivalents [79S633]. The most common of these is cyanide which affords acids by reactions of type **2.1** ⟶ **2.4** (Scheme 2.1). The preparation of α-hydroxy acids **2.9** from aldehydes and ketones **2.7** is most often carried out *via* cyanohydrins **2.8** (X = CN).



Scheme 2.1

Seebach [67AG(E)442] and Woessner [76CL43] have treated the lithio salts of orthothioformates **2.5** with alkyl halides or with carbonyl compounds to afford adducts

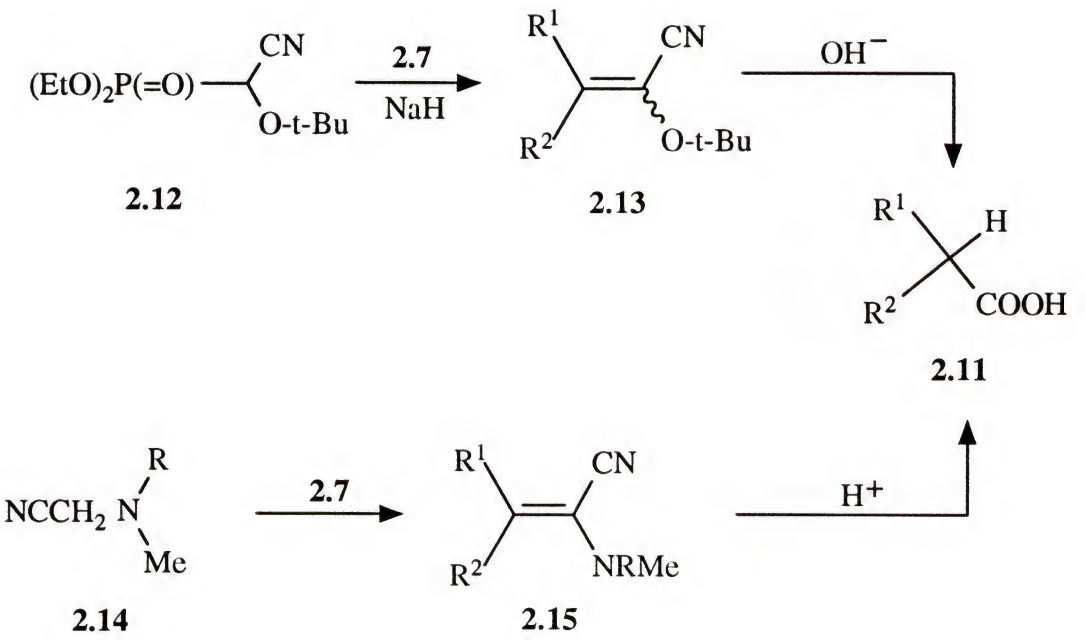
2.6 and **2.8**, respectively. Triphenylthiomethane [72CB487] and some of the trialkylthio [76TL2749] derivatives have also been employed, but few reports concern the synthetic utility of these derivatives as carboxylic acid [67AG(E)442] or ester [69AG(E)639] synthons.



2.7 **2.10** **2.11**

Scheme 2.2

Carbonyl compounds have also been converted into intermediates of type **2.10**, which on hydrolysis of both Z and Z' give acids (Scheme 2.2). Examples of intermediates of this type are: (i) ketene thioacetals [73CB2277; 72AG(E)526] **2.10** (Z, Z' = SR), (ii) α,β-unsaturated sulfones [72AG(E)311] **2.10** (Z = SO_2Ar, Z' = NHCHO), (iii) α,β-unsaturated phosphonates [68AG(E)391] **2.10** (Z = $PO(OEt)_2$, Z' = NMe_2), (iv) metallated trihalomethanes [68JOC2565; 77S852; 76S825; 74S724; 78JOC2702], (v) a Horner-Emmons modification of the Wittig reaction using the reaction of diethyl *t*-butoxy(cyano)methylphosphonate **2.12** with **2.7** to give α-*t*-butoxyacrylonitriles **2.13** which, when converted to the acetoxy derivatives, undergo basic hydrolysis to form carboxylic acids [77JA182], and (vi) aldehydes and benzophenone with N-cyanomethyl-N-methylaniline [83JOC3566] **2.14** (R = Ph) or aromatic aldehydes with N-cyanomethyl-N-methylamines [83S1043] **2.14** (R = H, R) to form α-cyanoenamides **2.15** which then undergo acidic hydrolysis to form carboxylic acids (Scheme 2.3).



2.12 **2.13** **2.11**

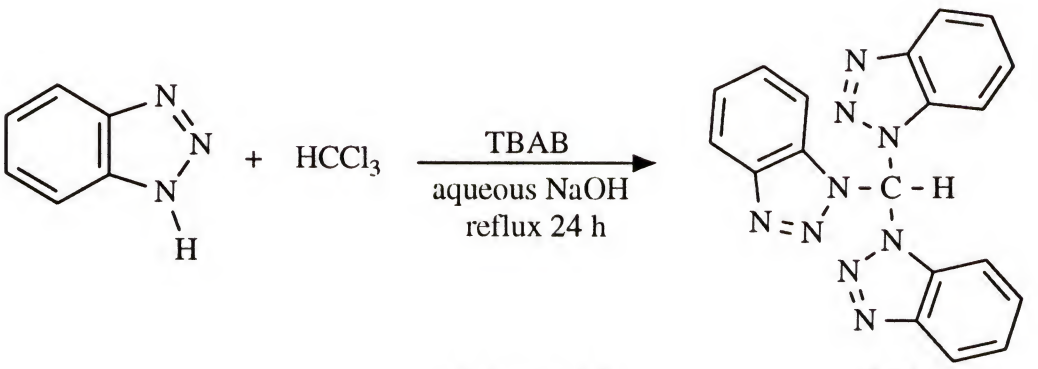
2.14 **2.15**

Scheme 2.3

Many of these methods involve inefficient hydrolyses of the intermediates or difficult syntheses of starting materials. For instance hydrolysis of cyano derivatives generally requires harsh reaction conditions, such as high temperatures and/or strong bases [56JOC1149; 70JOC2376]. The phosphonates **2.10** can be prepared only from aldehydes [68AG(E)391] and α-(N-aroyl-N-methylamino)acetonitriles **2.15** only from aromatic aldehydes [83S1043]. Bromoform reacts only with aromatic aldehydes using a combination of potassium hydroxide and lithium chloride [68JOC2565] or lithium amide [77S852] as catalyst. The thioacetals **2.10** (Z, Z' = SR) require the use of excess mercuric oxide and borontrifluoride etherate [76TL2749; 76TL1561] for their hydrolysis to the carboxylic acids. Some α-alkoxyacrylonitriles [77JA182] are difficult to hydrolyze. There is no general information as to the synthesis of α-cyanoenanamines [83JOC3566].

Tris(benzotriazol-1-yl)methane can be easily prepared by reaction of benzotriazole with chloroform in the presence of sodium hydroxide and

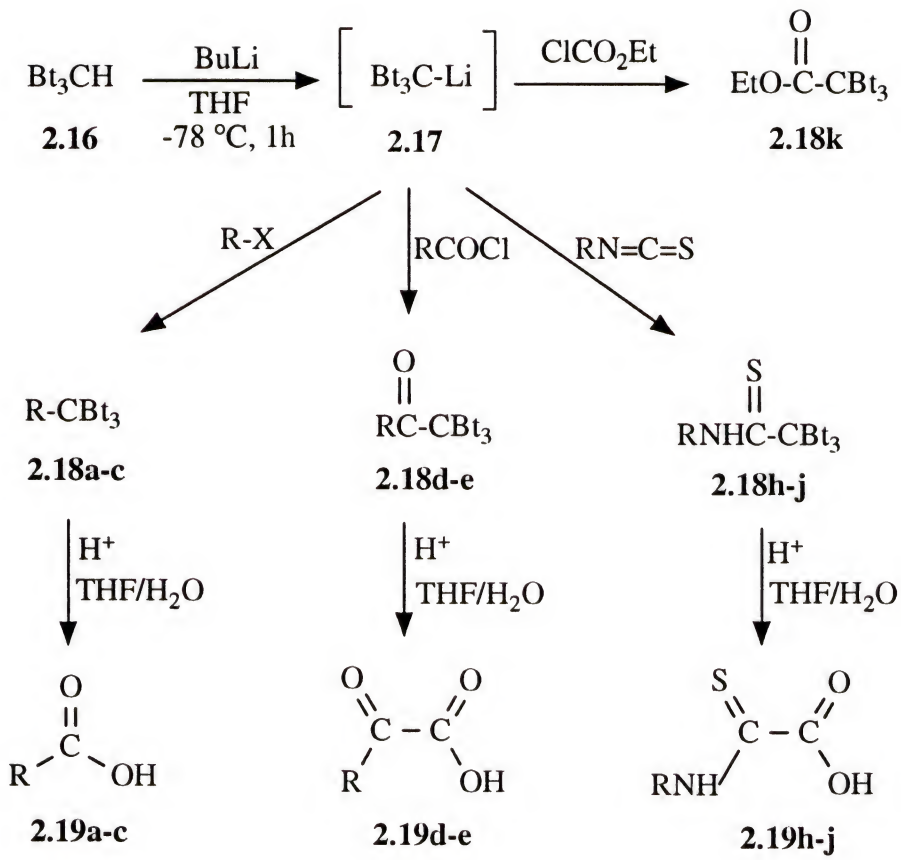
tetrabutylammonium bromide (TBAB) (Scheme 2.4). It is a stable, non-smelly, white solid, mp 194-196°C. As mentioned in the introduction, benzotriazole has been shown to be a good activating and leaving group, and therefore deprotonation of tris(benzotriazol-1-yl)methane and reaction with electrophiles should be highly possible. Subsequent hydrolysis of the resulting intermediate products should give the corresponding carboxylic acids with one-carbon elongation.



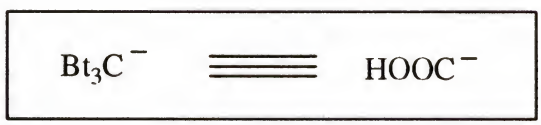
Scheme 2.4 **2.16**

2.2 Results and Discussion

The lithiation of tris(benzotriazol-1-yl)methane **2.16** occurs readily with *n*-butyllithium in a solution of tetrahydrofuran at -78 °C to afford anion **2.17**. Interestingly while the anions from the mono- [90HAC21] and bis- [87JCS(P1)819] benzotriazol-1-ylmethyl derivatives are dark blue in color, derivative **2.17** is pale yellow.



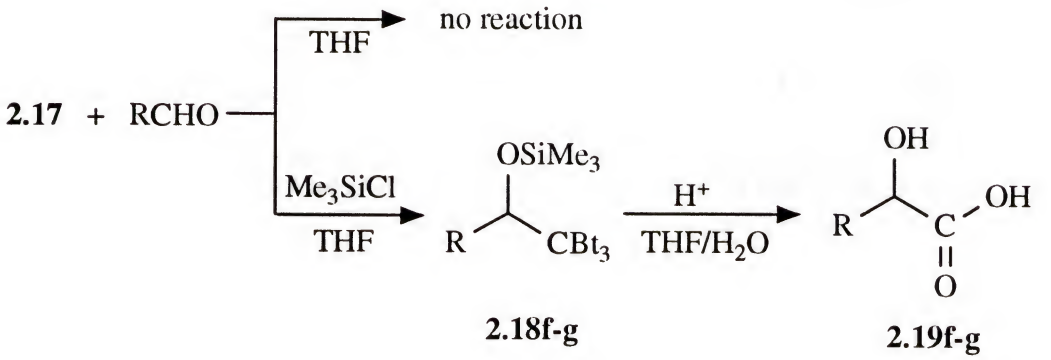
Bt = benzotriazol-1-yl



Scheme 2.5

The anion **2.17** reacts with alkyl and acyl halides, isothiocyanates and chloroformates to form the corresponding adducts **2.18** in high yields as shown in Scheme 2.5 and Table 2.1. The reaction of **2.17** with *p*-tolualdehyde resulted in recovery of the starting material. However, when trimethylsilyl chloride was added to the reaction mixture (after addition of the *p*-tolualdehyde), the corresponding silyl ether **2.18f** was obtained in excellent yield (Scheme 2.6). A similar pattern was also

observed in the reaction of *p*-[bis(benzotriazol-1-yl)methyl]toluene with aldehydes [87JCS(P1)819]. However, probably for steric reasons, the anion **2.17** did not react with secondary halides or with ketones.



2.18f-g **2.19f-g**

Scheme 2.6

The derivatives **2.18a-k** were characterized by ^{1}H and ^{13}C NMR spectroscopy and by their CHN analysis data (Tables 2.1-2.4). Absence of the methine signal at δ 10.2 and at 78.0 ppm, respectively, indicated complete reaction. The quaternary carbons were observed between 88.7 and 96.1 ppm, those attached to an electron deficient carbon atom resonated at the higher field end of this range. Six resonances were observed for the benzotriazole carbon atoms indicating no isomerization to the 2-substituted derivatives.

Treatment of the benzylated derivative **2.18a** at room temperature with 1M or 5M hydrochloric acid in tetrahydrofuran gave back only starting material. When the reaction solution was heated under reflux for 72 h, a mixture, including the starting material, was obtained. However, with concentrated sulfuric acid in tetrahydrofuran at 50°C for 24 h, hydrolysis of **2.18a** occurred smoothly: benzotriazole hydrogen sulfate precipitated and phenylacetic acid was obtained in 92% yield. Under similar conditions the corresponding α-keto, α-hydroxy, and other α-functionalized carboxylic acids were obtained in good yields (Table 2.5).

2.3 Experimental

Melting points were determined on a Bristoline hot-stage microscope and are uncorrected. ^1H (300 MHz) NMR spectra were recorded on a Varian VXR-300 spectrometer with Me_4Si as internal reference. ^{13}C NMR spectra were recorded at 75 MHz on the same instrument using solvent peaks ($CDCl_3$, δ 77.0 or DMSO-d_6, δ 39.5) as references. Microanalyses were obtained using a Carlo Erba 1106 elemental analyzer. Tetrahydrofuran (THF) was freshly distilled from sodium-benzophenone. All moisture sensitive reactions were carried out in a dry argon atmosphere.

2.3.1 Preparation of Tris(benzotriazol-1-yl)methane **2.16**

A mixture of benzotriazole (119 g, 1.0 mol), aqueous NaOH (40%, 100 mL), and tetrabutylammonium bromide (3.2 g) in $CHCl_3$ (100 mL) is heated under reflux for 48 h. The reaction mixture is cooled and the organic material extracted with $CHCl_3$ (2 x 100 mL). The organic layer is washed with water (5 x 25 mL), dried ($MgSO_4$) and concentrated at reduced pressure to give a brown solid. Trituration with methanol affords the pure product; yield: 60.5 g (50%); mp 194-196 °C; (Lit. [83H1787] mp 191 °C).

2.3.2 Lithiation of Tris(benzotriazol-1-yl)methane and Reaction with Electrophiles; General Procedure

n-BuLi (2.5M in hexane; 4.4 mL, 11 mmol) is added dropwise at -78°C to a solution of tris(benzotriazol-1-yl)methane (3.67 g, 10 mmol) in dry THF (80 mL). The mixture is stirred at -78°C for 1h, and then an appropriate electrophile (11 mmol) in THF (10 mL) is added (for the silyl derivatives **2.18f,g**, a solution of trimethylsilyl

chloride (11 mmol) in THF (10 mL) is added to the above solution 30 mins after addition of the aldehyde). The mixture is stirred at -78 °C for 5 h, and then at ambient temperature for 12 h. The reaction mixture is poured into saturated aqueous NH_4Cl (40 mL), and the aqueous layer extracted with $CHCl_3$ (3 x 25 mL). The combined organic layers are washed with water (1 x 25 mL), dried ($MgSO_4$) and the solvent removed at reduced presure to afford the crude adducts which are then recrystallized to give analytically pure products **2.18a-k** (Tables 2.1-2.4).

2.3.3 Hydrolysis of Compounds **2.18a-j**; General Procedure

To a stirred solution of the trisbenzotriazolyl derivative (2 mmol) in THF (20 mL) is added concentrated sulfuric acid (95-98%; 0.5 mL) and the solution stirred at 50 °C for 24 h. Benzotriazole is filtered off and the filtrate evaporated at reduced pressure to give an oil. Water (5 mL) is added and the mixture extracted with Et_2O (3 x 10 mL). The combined ethereal extracts are washed with cold water (2 x 5 mL), and dried ($MgSO_4$). Evaporation of the solvent gives the crude products which are then purified accordingly to afford the carboxylic acids **2.19a-j** (Table 2.5).

Phenylthiooxamic Acid **2.19h**: yellow needles from cyclohexane, mp 95-96°C. ^1H NMR ($CDCl_3$/TMS): 10.86 (s, 1 H); 8.0-7.8 (m, 2 H); 7.5-7.35 (m, 3 H). ^{13}C NMR ($CDCl_3$): 178.0, 158.5, 137.1, 129.3, 128.1, 121.5. *Analysis* ($C_8H_7NO_2S$): calcd: C 53.04 H 3.87 N 7.73; found: C 53.02 H 3.84 N 7.73.

1-Naphthylthiooxamic Acid **2.19i**: yellow needles from cyclohexane, mp 118-120°C. ^1H NMR ($CDCl_3$/TMS): 11.19 (s, 1 H); 8.32-8.28 (m, 1 H); 7.9-7.5 (m, 7 H). ^{13}C NMR ($CDCl_3$): 180.4, 158.5, 134.0, 132.2, 129.0, 128.9, 127.4, 126.9, 126.7, 125.2, 121.1, 120.1. *Analysis* ($C_{12}H_9NO_2S$): calcd: C 62.34 H 3.90 N 6.06; found: C 62.58 H 4.00 N 5.95.

Benzylthiooxamic Acid **2.19j**: yellow oil (Found M^+ m/z 195.0358; $C_9H_9NO_2S$ requires M^+ m/z 195.0354). ^1H NMR ($CDCl_3$/TMS): 9.65 (bs,1 H); 9.50 (bs, 1 H); 7.27 (s, 5 H); 4.72 (d, 2 H, J = 6 Hz). ^{13}C NMR ($CDCl_3$): 182.5, 158.0, 134.1, 128.6, 128.1, 128.0, 50.6.

Table 2.1 Reaction of Bt_3CH with butyllithium and electrophiles

Compd	Electrophile	Yield (%)	mp (°C)	Recrys. solvent
2.18a	$PhCH_2Br$	92	120-122	MeOH
2.18b	$PhCH{=}CHCH_2Br$	84	145-147	EtOH
2.18c	n-BuI	86	172-174	MeOH
2.18d	PhCOCl	98	265-267	MeOH
2.18e	$4\text{-}MeC_6H_4COCl$	98	263-265	Me_2CO
2.18f	$PhCHO/ClSiMe_3$	91	190-191	MeOH
2.18g	$4\text{-}MeC_6H_4CHO/ClSiMe_3$	94	205-207	MeOH
2.18h	PhNCS	90	200-201	Me_2CO
2.18i	$1\text{-}C_{10}H_7NCS$	89	205-207	Me_2CO
2.18i	$PhCH_2NCS$	80	195-197	Me_2CO
2.18k	ClCOOEt	95	215-217	EtOAc

Table 2.2 ^{1}H NMR data of adducts **2.18a-k**

2.18a	8.06 (d, 3H, J=7.4Hz), 6.75-7.4 (m, 14H), 5.39 (s, 2H)
2.18b	8.0-8.1 (m, 3H), 7.3-7.4 (m, 6H), 7.08-7.15 (m, 6H), 6.8-6.9 (m, 1H), 5.92 (d, 1H, J=14.6Hz), 4.81 (d, 1H, J=7.1)
2.18c	8.05-8.1 (m, 3H), 7.3-7.4 (m, 6H), 7.07-7.12 (m, 3H), 3.3.9-4.0 (m, 2H), 1.25-1.45 (m, 4H), 0.78 (t, 3H, J=7Hz)
2.18d	8.00-8.05 (m, 3H), 7.70-7.75 (m, 2H), 7.15-7.4 (m, 9H), 6.9-7.0 (m, 3H)
2.18e	8.00-8.05 (m, 3H), 7.62 (d, 2H, J=8.5Hz), 7.20-7.35 (m, 6H), 6.9-7.0 (m, 5H), 2.21 (s, 3H)
2.18f	8.0-8.1 (m, 3H), 7.81 (s, 1H), 7.1-7.4 (m, 10H), 6.9-7.0 (m, 4H), -0.21 (s, 9H)
2.18g	7.9-8.1 (m, 3H), 7.83 (s, 1H), 7.1-7.4 (m, 9H), 6.7-6.8 (m, 4H), 2.17 (s, 3H), -0.22 (s, 9H)
2.18h	8.75-8.8 (m, 3H), 7.9-8.15 (m, 14H), 7.15-7.4 (bs, 1H)
2.18i	8.5-8.8 (m, 4H), 8.25-8.4 (m, 2H), 7.7-8.0 (m, 11H), 6.95-7.45 (m, 3H)
2.18j	11.86 (m, 1H), 8.19 (m, 3H), 7.2-7.6 (m, 11H), 6.60-6.65 (m, 3H), 5.00 (d, 2H, J=5.4Hz)
2.18k	8.07-8.10 (m, 3H), 7.3-7.4 (m, 6H), 6.9-7.0 (m, 3H), 4.51 (q, 2H, J=7.1Hz), 1.15 (m, t, J=7.1Hz)

Table 2.3 ^{13}C NMR data of adducts **2.18a-k**

Compd	Bt	*tert*-C	E
2.18a	146.8 132.6 128.8 124.9 120.5 112.4	94.1	130.9 130.6 128.3 128.28 44.77
2.18b	146.8 132.2 128.9 125.0 120.5 111.8	92.9	137.0 135.6 128.2 127.8 126.1 118.9 43.15
2.18c	146.6 132.0 128.9 124.9 120.4 111.6	93.3	39.2 25.4 21.9 13.4
2.18d	146.4 133.2 129.5 125.3 120.4 111.4	91.0	182.9 134.6 132.6 129.9 128.5
2.18e	146.4 133.2 129.4 125.2 120.3 111.5	91.1	182.3 146.0 130.1 129.3 21.6
2.18f	146.5 133.0 128.2 124.8 120.0 113.8	96.0	135.5 129.2 128.9 127.7 78.7 0.1
2.18g	146.5 133.0 128.2 124.7 120.0 113.8	96.1	139.1 132.4 128.8 128.4 78.6 21.0 0.0
2.18h	145.7 134.0 129.0 124.7 120.1 112.0	93.2	182.8 128.7 129.5 127.7 125.3
2.18i	145.8 133.9 129.6 125.6 120.2 112.1	93.4	185.7 136.0 134.0 128.6 128.5 128.2 126.6 126.5 125.4 124.0 123.7
2.18j	145.7 133.9 128.4 125.2 120.0 112.0	92.9	183.8 125.9 129.3 128.1 127.4 51.3
2.18k	146.5 133.0 129.3 125.2 120.4 111.3	88.7	160.9 65.7 13.5

Table 2.4 Microanalyses data for adducts **2.18a-k**

Compd	Molecular formula	C	H	N	C	H	N
		required (%)			found (%)		
2.18a	$C_{26}H_{19}N_9$	68.27	4.16	27.97	67.88	4.09	27.97
2.18b	$C_{28}H_{21}N_9$	69.57	4.35	26.09	69.41	4.44	26.52
2.18c	$C_{23}H_{21}N_9$	65.25	4.96	29.79	65.07	4.93	30.29
2.18d	$C_{26}H_{17}N_9O$	66.24	3.61	26.75	66.08	3.56	27.17
2.18e	$C_{27}H_{19}N_9O$	66.80	3.92	25.98	66.69	3.96	26.04
2.18f	$C_{29}H_{27}N_9OSi$	63.85	4.95	23.12	63.73	5.06	23.50
2.18g	$C_{29}H_{29}N_9OSi$	64.40	5.19	22.54	64.40	5.27	22.95
2.18h	$C_{26}H_{18}N_{10}S$	62.35	3.59	27.89	61.95	3.55	28.33
2.18i	$C_{30}H_{20}N_{10}S$	65.22	3.62	25.26	65.32	3.67	25.67
2.18j	$C_{27}H_{20}N_{10}S$	62.79	3.88	27.13	62.58	3.78	27.42
2.18k	$C_{22}H_{17}N_9O_2$	60.14	3.87	28.90	60.08	3.88	29.06

Table 2.5 Preparation of Carboxylic acids **2.19a-j**

Entry	Compd	Yield (%)	mp (°C)	Lit. mp (°C)
2.19a	$PhCH_2COOH$	92	76-77	76-76.5[a]
2.19b	$PhCH{=}CHCH_2COOH$	73	85-86	87[b]
2.19c	*n*-BuCOOH	79	85-87[h]	80-83[c,i]
2.19d	PhCOCOOH	81	62-64	61-64[d]
2.19e	$4\text{-}MeC_6H_4COCOOH$	83	94-95	91-93[e]
2.19f	PhCH(OH)COOH	78	117-118	115-117[f]
2.19g	$4\text{-}MeC_6H_4CH(OH)COOH$	76	144-145	145-145.5[g]
2.19h	PhNHC(=S)COOH	82	95-96	-- --
2.19i	$1\text{-}C_{10}H_7NHC(=S)COOH$	87	118-120	-- --
2.19j	$PhCH_2NHC(=S)COOH$	74	Oil	-- --

[a] [41OS436]. [b] [26JCS2735]. [c] [78S462]. [d] [81JOC211]. [e] [81JOC211].

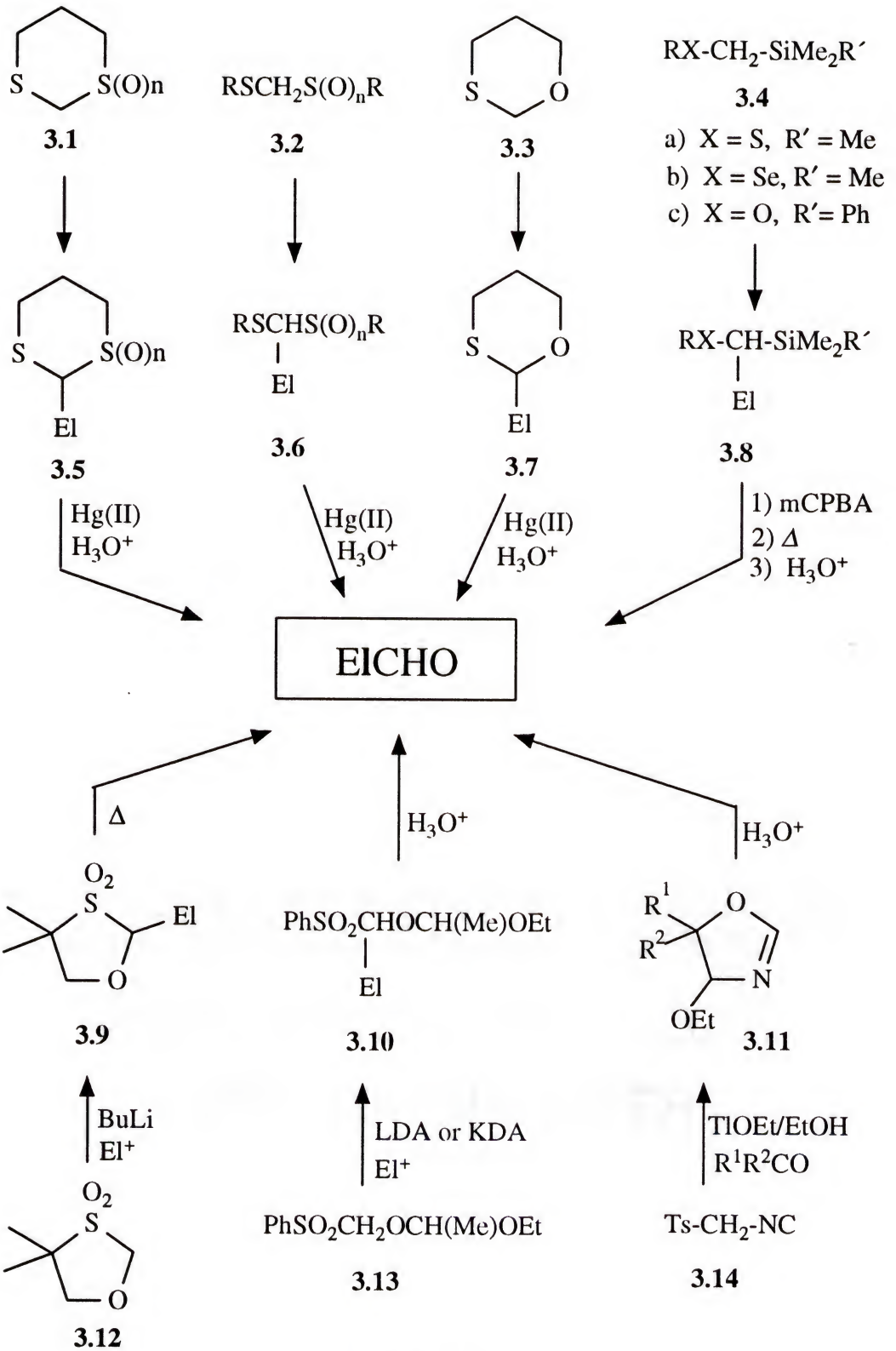
[f] [55OS538]. [g] [38JA1015]. [h] Bp/15mmHg. [i] Bp/10mmHg.

CHAPTER III
(BENZOTRIAZOL-1-YL)(CARBAZOL-9-YL)METHANE: A NOVEL FORMYL SYNTHON EQUIVALENT

3.1 Introduction

As lack of stability greatly limits the use of formyl ($^-$CH=O) and acyl ($^-$CR=O) anions [81JA5612], various masked synthons have been developed [87MI1]. Important formyl anion equivalents are of the type XYCH$^-$ where X and Y are heteroatoms (Scheme 3.1). Dithioformyls employed include the 1,3-dithiane [78S713; 77S357] (**3.1; n = 0**), and bis(alkylthio)- [59RTC663] (**3.2; R = alkyl, n = 0**), bis(arylthio)- [66JOC4097] (**3.2; R = Ar, n = 0**), and cyclic [75S720] analogs. Thioacetals with one sulfur atom oxidized (*e.g.*, **3.1, 3.2; n = 1**) have also been used [71TL3151]. Reaction of anions, generated by *e.g.* treatment with *n*-butyllithium [75JOC231], or by lithium or sodium amide in liquid ammonia [59RTC663], with electrophiles gives the corresponding thioacetals **3.5** and **3.6** which are converted to the aldehydes by complex formation with a metal ion (usually mercury (II) salts [67JA431; 67JA434]) or by making one sulfur atom more electrophilic through oxidation [82TL3949].

Other sulfur analogs used include 1,3-oxathianes **3.3** [85JOC657], α-thiosilanes **3.4a** [80TL1559], α-functionalized sulfones **3.12, 3.13** [79TL3375; 80BCSJ3619] and TosMIC **3.14** [73TL629; 74TL163; 74TL167]. Oxidation of **3.8** followed by a Sila-Pummerer rearrangement affords the O-trimethylsilylthioacetal [83JCS(P1)1131]; hydrolysis by acid or base then affords the aldehydes. Similarly to the α-thiosilanes, phenylselenotrimethylsilylmethane **3.4b** has been used [76TL4223]. Reaction of methoxy(phenyldimethylsilyl)methyllithium [89JCS(C)1256] with carbonyl compounds has afforded β-hydroxysilanes which were converted to the


S S(O)n
3.1
RSCH2S(O)nR
3.2
S O
3.3
RX-CH2-SiMe2R´
3.4
a) X = S, R′ = Me
b) X = Se, R′ = Me
c) X = O, R′= Ph
S S(O)n
El
3.5
RSCHS(O)nR
El
3.6
S O
El
3.7
RX-CH-SiMe2R´
El
3.8
Hg(II)
H3O+
Hg(II)
H3O+
Hg(II)
H3O+
1) mCPBA
2) Δ
3) H3O+
ElCHO
Δ
H3O+
H3O+
O2
S
El
O
3.9
PhSO2CHOCH(Me)OEt
El
3.10
R1
R2
O
N
OEt
3.11
BuLi
El+
LDA or KDA
El+
TlOEt/EtOH
R1R2CO
O2
S
O
3.12
PhSO2CH2OCH(Me)OEt
3.13
Ts-CH2-NC
3.14

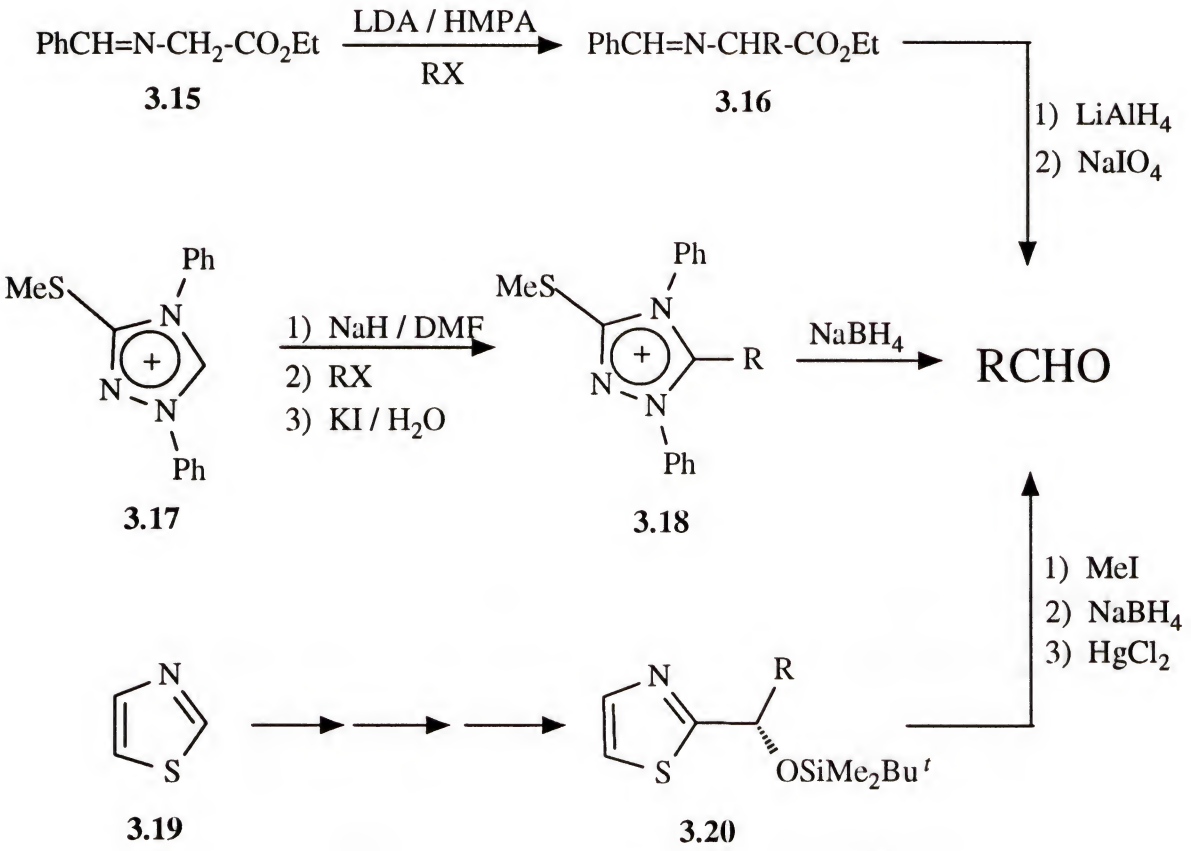
Scheme 3.1

α-hydroxyaldehydes by acetic anhydride, hydrogen peroxide, *m*-chloroperbenzoic acid and bromine, or potassium bromide.

These reactions are subject to various limitations. The anions of hemithioacetals **3.3** react readily with alkyl iodides, but yields with bromides and other types of electrophiles are low to moderate [85JOC657]. The α-thiosilanes **3.4a** react only with a limited number of electrophiles to afford **3.8**, since with carbonyl compounds vinyl sulfides are obtained [72JOC939]. For the α-functional sulfones **3.12**, only the alkyl derivatives **3.9** have been converted to the aldehydes *via* pyrolysis [79TL3375]. Few examples are known of the linear analogs **3.13** which require KDA instead of LDA for condensation with carbonyl compounds [80BCSJ3619]. TosMIC **3.14** undergoes alkylation under phase-transfer conditions [83SC331; 83SC1067], but for reaction with carbonyl compounds, thallium ethoxide is required to form the oxazoline **3.11** which is hydrolyzed to the α-hydroxyaldehyde [73TL629; 74TL163; 74TL167]. Recently BetMIC (1-benzotriazolylmethyl isocyanide) used in place of TosMIC, did not need thallium for the preparation of α-hydroxyaldehydes [89TL6657].

Another class of formyl anion equivalents, $X(Y:)C^-$ (Scheme 3.2), requires a subsequent reduction step. They include the substituted imines [76JOC3491] **3.15** which react with alkyl halides forming intermediates **3.16**; subsequent reduction with lithium aluminum hydride and sodium periodate gives modest yields of the aldehydes [76JOC3491]. 3-Methylthio-1,4-diphenyl-*s*-triazolium iodide [75TL1889] **3.17** reacts with alkyl halides; reduction of the products with sodium borohydride then affords the aldehydes. However, use of both of these reagents is apparently limited to reactions with alkyl halides as electrophiles. Dondoni [89T5141] *et al.* have used thiazole **3.19** which affords a high level of diastereoselectivity during the reduction of acylthiazoles containing an α-chiral center [89JOC693]. Deprotection is a one-pot operation

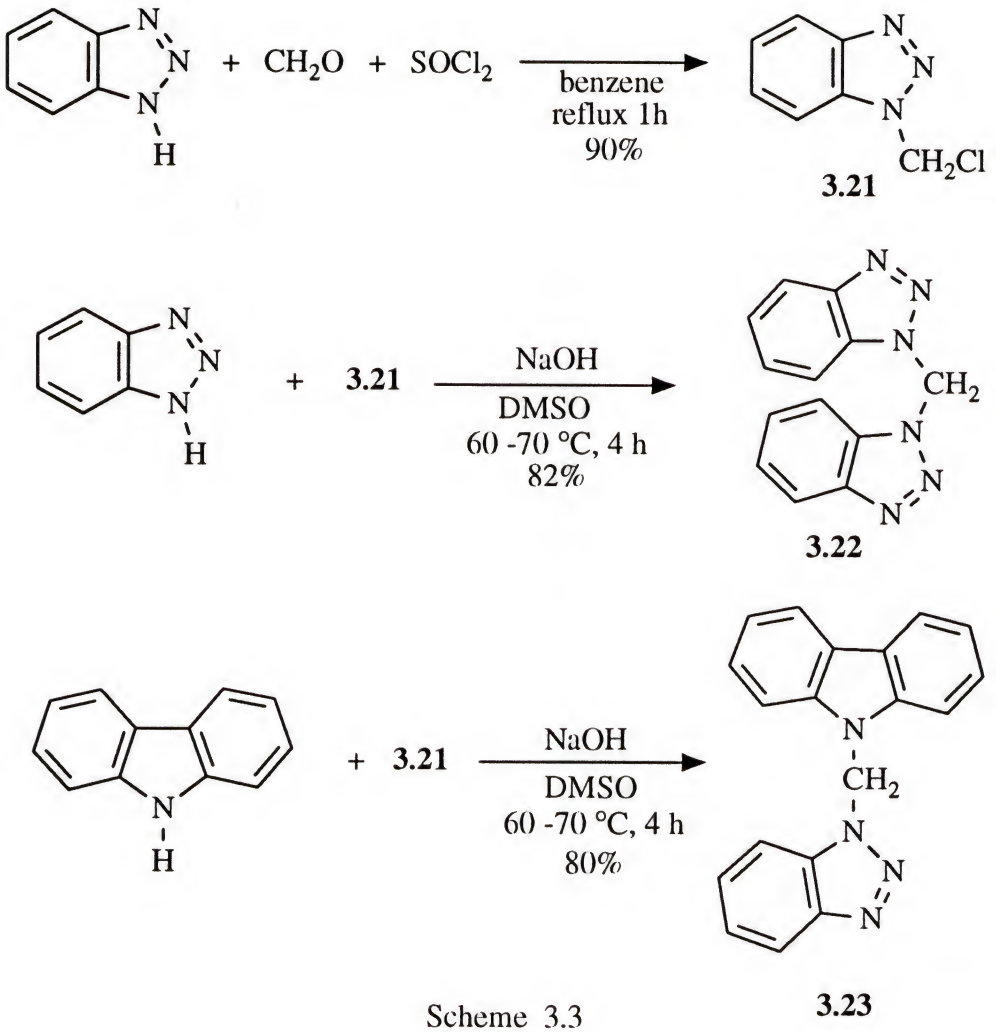
requiring a sequence of reagents (methyl iodide, reflux; sodium borohydride, -10 °C; and finally mercury (II) chloride).



Scheme 3.2

As mentioned previously, a formyl carbon is usually attached to two heteroatoms. However, little attention has been paid to systems where the two heteroatoms are parts of separate heterocycles.

Considering our work with tris(benzotriazol-1-yl)methane, it is expected that bis(benzotriazol-1-yl)methane should similarly function as a formyl synthon equivalent. Bis(benzotriazol-1-yl)methane and other heterocycle analogues can be easily prepared by the reaction of 1-chloromethylbenzotriazole with benzotriazole or other appropriate heterocycles in the presence of base [89JHC829] (Scheme 3.3).

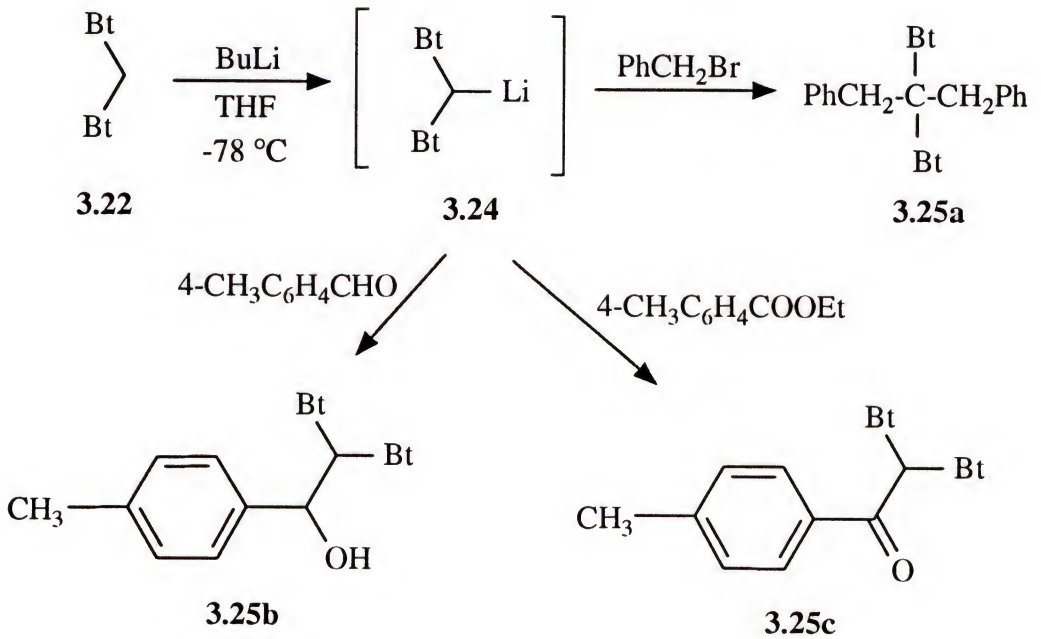


Scheme 3.3

3.2 Results and Discussion

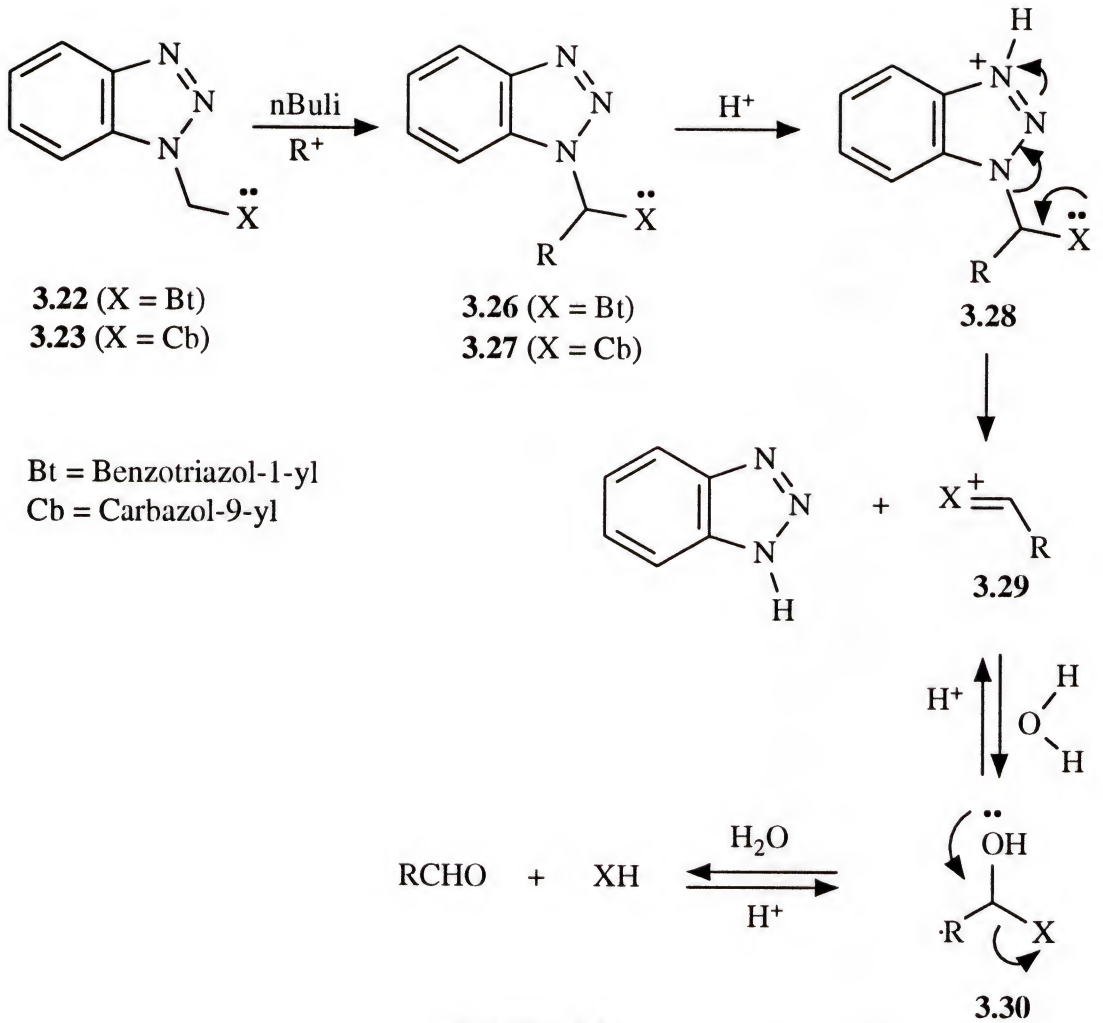
Bis(benzotriazol-1-yl)methane **3.22** underwent smooth lithiation with *n*-butyllithium at -78 °C and the anion reacted with benzyl bromide and carbonyl compounds to form the corresponding adducts **3.25a-c** (Scheme 3.4) in yields of 46-76% (see Table 3.1). However, attempts to hydrolyze the adducts **3.25a-c** using conditions ranging from 1M to 10M hydrochloric acid in tetrahydrofuran, reflux

conditions or using 55% sulfuric acid failed to generate the aldehydes (or in the case of **3.25a**, the ketone) satisfactorily.



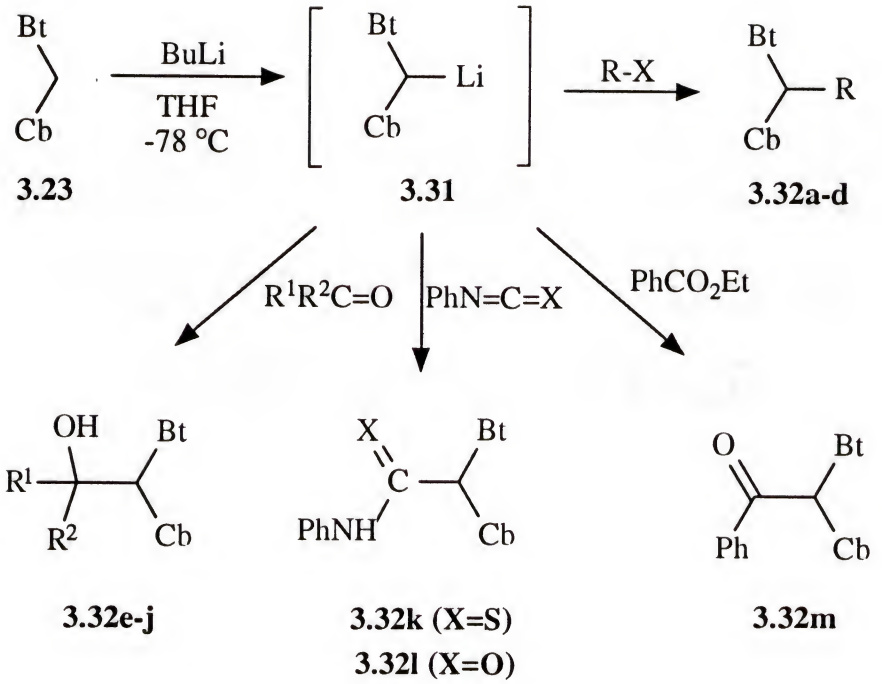
Scheme 3.4

Benzotriazole is electron-withdrawing in nature and evidently there is insufficient electronic assistance from the one benzotriazole moiety to the elimination of the other protonated benzotriazole from the intermediate **3.28** (Scheme 3.5) when R = alkyl or acyl, in contrast to the success of such hydrolysis when R = aryl [87JCS(P1)819] as mentioned above.



Scheme 3.5

Based on this rationalization, we selected carbazole as the other heterocycle, which with a greater electron donor effect should assist in the displacement of benzotriazole without simultaneous deactivation of the methylene group towards deprotonation (Scheme 3.5). Indeed, (benzotriazol-1-yl)(carbazol-9-yl)methane **3.23** readily underwent lithiation and reaction with a wide range of alkyl halides, aldehydes, ketones, esters, isocyanates, and isothiocyanates to form the corresponding products in good yields (Scheme 3.6 and Table 3.1).

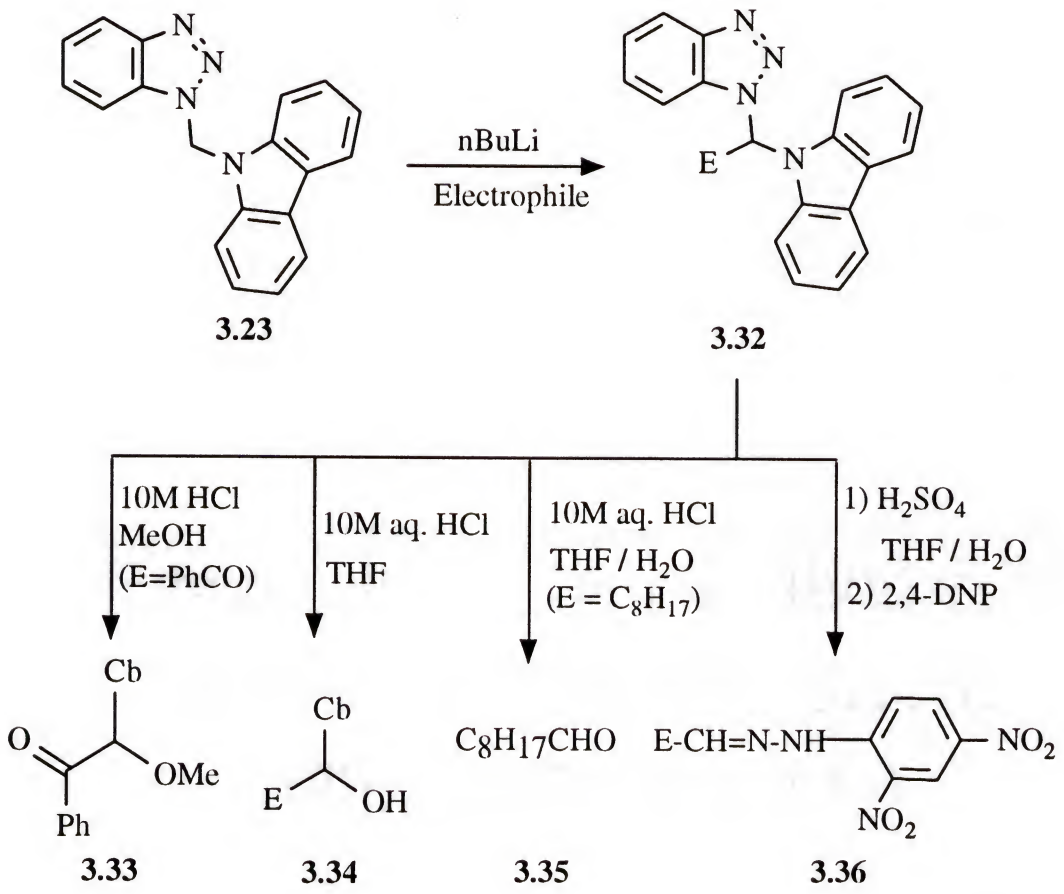


Scheme 3.6

The reaction of (benzotriazol-1-yl)(carbazol-9-yl)methane **3.23** with *n*-butyllithium at -78 °C in tetrahydrofuran yielded a pale yellow solution of the anion. Subsequent treatment with various electrophiles (see Table 3.1) yielded 71-96% of pure crystalline products which were characterized by their microanalyses data and ^{1}H and ^{13}C NMR spectra (Tables 3.2-3.4). Absence of the methylene carbon resonance at 54.4 ppm in the ^{13}C NMR spectra of the crude products indicated that the reactions went to completion. The corresponding methine carbons of the products resonated downfield between 67 and 75 ppm.

Hydrolysis of the benzoyl derivative **3.32m** with 4 equivalents of 10M hydrochloric acid in methanol afforded 9-(α-methoxyphenacyl)carbazole **3.33** as a colorless oil (Scheme 3.7). The ^{1}H and ^{13}C NMR spectra displayed signals corresponding to carbazole, but indicated the absence of the benzotriazole group. The

presence of a new singlet at 3.25 ppm in the proton spectrum and at 55.8 ppm in the carbon spectrum indicated displacement of benzotriazole by the methoxy group forming **3.33**.



Scheme 3.7

When methanol was replaced by tetrahydrofuran, the NMR of the unstable product indicated it to be N-(α-hydroxyphenacyl)carbazole (**3.34;** E = PhCO). The absence of benzotriazole resonances and the downfield shift of the N-C_a carbon to 87.9 ppm confirmed the suspicion. For the benzyl derivative (**3.34;** E = $PhCH_2$), in addition to the similar downfield shift of the N-C_a carbon in the ^{13}C NMR spectrum,

an aldehyde resonance at 193.8 ppm was also detected. The corresponding aldehyde signal at 9.6 ppm in the ^{1}H NMR indicated that it was formed in *ca.* 45% yield.

Such adducts of carbazole with aldehydes have not previously been reported. However, Anfinogenov *et al.* [79JOC(USSR)1605] treated carbazole with aliphatic aldehydes and alcohols in acid to give the carbenium- immonium ion **3.29** in the slow step which was then reacted with the alcohols.

The isolation of **3.34** is in agreement with our findings involving attack of methanol on **3.29** affording **3.33**. In tetrahydrofuran, the semiaminal **3.34** was the major product (obviously from the small amount of water present in the 10M HCl solution). A larger amount of water shifted the equilibrium further, affording the aldehyde in a yield of 40%. From the octyl derivative **3.32c**, the corresponding nonyl aldehyde **3.35** was isolated (57%). The other aldehydes were trapped prior to isolation. Thus treatment of the adducts with concentrated sulfuric acid in THF/H_2O (2:1) in the presence of 2,4-dinitrophenylhydrazine (DNP), or addition of DNP in 10% perchloric acid to the reaction solution after 24h, afforded the corresponding hydrazones **3.36a-l** in yields of 61-83% (Table 3.5). The hydrazones were characterized by their ^{1}H and ^{13}C NMR spectra and by their CHN analyses (see Tables 3.5-3.8).

The single step used in the present procedure makes it more attractive than those requiring multiple steps for the formation of the aldehydes. Our use of aqueous acid is also preferable to mercury reagents, thermolysis or strong reducing agents. Oxidized thioacetals are indeed hydrolyzed under mild acid conditions; however, hydrolysis of some of these adducts afforded α-hydroxyketones (*i.e.* $ArCOCH_2OH$ rather than the expected ArCH(OH)CHO), although copper(II) chloride or triethyl orthoformate circumvented this problem [72TL2681]. The hydrolysis of the TosMIC oxazole does occur with dilute hydrochloric acid in THF at room temperature, but this method is applicable only to α-hydroxyaldehydes.

The (benzotriazol-1-yl)(carbazol-9-yl)methane system, which is the first formyl synthon equivalent developed from a heterocycle-activated methane, is attractive due to the relatively mild single-step hydrolysis conditions employed and the variety of electrophiles that can be utilized.

3.3 Experimental

Melting points were determined on a bristoline hot-stage microscope and are uncorrected. ^{1}H (300 MHz) NMR spectra were recorded on a Varian VXR-300 (FT mode) spectrometer with Me_4Si as internal standard. ^{13}C NMR spectra were recorded at 75 MHz on the same instrument using solvent peaks ($CDCl_3$, δ 77.0 or DMSO-d_6, δ 39.5) as references. Elemental analyses (CHN) were carried out using a Carlo Erba 1106 elemental analyzer. Tetrahydrofuran (THF) was freshly distilled from sodium-benzophenone. All moisture sensitive reactions were carried out in a dry argon atmosphere. The following compound was prepared by a known literature procedure: Bis(benzotriazol-1-yl)methane **3.22**, mp 191-193°C, lit. [73JA3868] mp 192-193°C.

3.3.1 Preparation of (Benzotriazol-1-yl)(carbazol-9-yl)methane (**3.23**)

To a solution of carbazole (6.7 g, 40 mmol) in DMSO (30 mL) was added powdered NaOH (3.2 g, 80 mmol). The mixture was heated to 50-60 °C and kept for 2 h at this temperature. 1-Chloromethylbenzotriazole (6.7 g, 40 mmol) was added to the above solution and the mixture stirred for an additional 2 h at 50-60°C. After cooling, the reaction mixture was poured into ice (100 g), and the precipitate was filtered off, washed with water (3 x 50 mL) and dried. The pale solid thus obtained was triturated

with benzene to give the pure product (12 g, 80%), mp 193-195°C, lit. [89JHC829] mp 194-196°C.

3.3.2 General procedure for the lithiation of bis(benzotriazol-1-yl)methane (**3.22**) and (benzotriazol-1-yl)(carbazol-9-yl)methane (**3.23**) and reaction with electrophiles

To a solution of **3.22** or **3.23** (10 mmol) in dry THF (80 mL) was added *n*-BuLi (2.5M in hexane; 4.4 mL, 11 mmol) at -78 °C. The solution was stirred at -78 °C for 2 h and then an appropriate electrophile (11 mmol) in THF (10 mL) was added. The mixture was stirred at -78 °C for 4 h and then at room temperature for 12 h. The reaction mixture was poured into saturated aqueous NH_4Cl (40 mL), and the aqueous layer extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with water (1 x 25 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to afford the crude products which were then purified to give analytically pure products (Tables 3.1-3.4).

3.3.3 General procedure for the hydrolysis of the intermediates **3.32a-l**

Method A: To a solution of the intermediate **3.32** (2.5 mmol) in THF (20 mL) and H_2O (10 mL) was added conc. H_2SO_4 (0.5 mL). The solution was stirred at room temperature for 30 min and then 2,4-dinitrophenylhydrazine (2.5 mmol) was added. The mixture was stirred at room temperature for 24 h and extracted with Et_2O (3 x 25 mL). The etheral layer was dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow solid which was then recrystallized from appropriate solvents to afford the pure product (Tables 3.5-3.8).

Method B: The hydrolysis conditions were similar to Method A, but 2,4-dinitrophenylhydrazine in 10% $HClO_4$ was added to the reaction solution which had been previously stirred at room temperature for 24 h (Tables 3.5-3.8).

9-(α-Methoxyphenacyl)carbazole **3.33** A mixture of 1-[(benzoyl)-(carbazol-9-yl)methyl]benzotriazole **3.32m** (1.0 g, 2.4 mmol), 10 M HCl (0.5 mL) and MeOH (30 mL) was heated under reflux for 3 h. Evaporation of the solvent gave an oil which was extracted with Et_2O (2 x 25 mL), the combined organic layer washed with water (3 x 5 mL) and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure afforded an oil which was purified by column chromatography (chlorform/hexane: 2/1) to give the product as a pale yellow oil (0.66 g, 87%). ^1H NMR ($CDCl_3$): 8.0-7.75 (m, 4H), 7.6-7.05 (m, 9H), 6.73 (s, 1H), and 3.25 (s, 3H). ^{13}C NMR ($CDCl_3$): 191.6, 196.4, 134.1, 133.5, 128.2, 126.1, 123.7, 120.3, 120.2, 84.5, 55.8. HRMS: $C_{21}H_{17}N_{10}O_2$ requires M^+ *m/z* 315.1259; Found M^+ *m/z* 315.1252.

Nonyl Aldehyde **3.35** The octyl derivative **3.32c** (2.0 g, 4.88 mmol) was dissolved in THF (30 mL) and then HCl (10 M; 2 mL) and H_2O (15 mL) were added. The solution was stirred at ambient temperature for 24h. Et_2O (30 mL) was then added and the layers separated. The aqueous fraction was extracted with Et_2O (3 x 25 mL) and the combined organic fractions washed with water (2 x 15 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was extracted with hexanes (4 x 25 mL) and the solvent removed under reduced pressure. The crude product was then purified by column chromatography (hexane-$CHCl_3$, 2:1) to give 0.4 g (57%) of **3.35** as a colorless liquid: bp 77-79 °C/15 mm Hg, (lit. [40JA2305] bp 49-52 °C/1 mm Hg).

Table 3.1 Preparation of adducts **3.25a-c** and **3.32a-m**

Compd	Electrophile	Yield (%)	mp (°C)	Recrys. solvent
3.25a	$PhCH_2Br$	46	182-184	MeOH
3.25b	$4\text{-}MeC_6H_4CHO$	70	197-199	MeOH
3.25c	$4\text{-}MeC_6H_4CO_2Et$	76	181-183	MeOH
3.32a	$PhCH_2Br$	81	129-130	MeOH
3.32b	$4\text{-}BrC_6H_4CH_2Br$	78	141-142	MeOH
3.32c	$n\text{-}C_8H_{17}Br$	71	112-114	a
3.32d	$n\text{-}C_4H_9Br$	84	135-137	MeOH
3.32e	$4\text{-}MeC_6H_4CHO$	82	234-235	MeOH
3.32f	$(CH_3)_2CHCHO$	91	222-224	MeOH
3.32g	$(CH_3)_3CCHO$	96	218-220	MeOH/AcOEt
3.32h	$(C_2H_5)_2CO$	86	154-156	P.E./Ether
3.32i	$(CH_2)_5CO$	91	194-196	MeOH
3.32j	$(CH_2)_4CO$	84	197-198	MeOH
3.32k	PhNCS	78	178-179	MeOH/AcOEt
3.32l	PhNCO	93	201-202	MeOH
3.32m	$PhCO_2Et$	88	89-90	P.E./Ether

[a] Column chromatography (hexane : chloroform = 1 : 1).

3.2 Microanalyses data of adducts **3.25a-c** and **3.32a-m**

Compd	Molecular formula	C H N required (%)	C H N found (%)
3.25a	$C_{27}H_{22}N_6$	75.33 5.15 19.52	75.01 5.10 19.95
3.25b	$C_{21}H_{18}N_6O$	68.11 4.86 22.70	67.89 4.88 22.82
3.25c	$C_{21}H_{16}N_6O$	68.48 4.35 22.83	68.41 4.26 22.93
3.32a	$C_{26}H_{20}N_4$	[89JHC829]	
3.32b	$C_{26}H_{19}BrN_4$	66.82 4.10 11.99	66.56 4.06 11.80
3.32c	$C_{27}H_{30}N_4$	79.02 7.32 13.66	79.41 7.21 13.38
3.32d	$C_{23}H_{22}N_4$	77.97 6.21 15.82	77.90 6.23 15.89
3.32e	$C_{27}H_{22}N_4O$	[89JHC829]	
3.32f	$C_{23}H_{22}N_4O$	[89JHC829]	
3.32g	$C_{24}H_{24}N_4O$	75.00 6.25 14.58	75.35 6.41 14.70
3.32h	$C_{24}H_{24}N_4O$	74.97 6.29 14.57	74.68 6.34 14.55
3.32i	$C_{25}H_{22}N_4O$	75.73 6.10 14.13	75.85 6.18 14.27
3.32j	$C_{24}H_{22}N_4O$	75.37 5.80 14.65	75.34 5.78 14.96
3.32k	$C_{26}H_{19}N_5S$	72.03 4.42 16.15	72.14 4.37 16.29
3.32l	$C_{26}H_{19}N_5O$	74.80 4.59 16.78	74.52 4.51 16.84
3.32m	$C_{26}H_{18}N_4O$	[89JHC829]	

Table 3.3 ^{1}H NMR data of adducts **3.25a-c** and **3.32a-m**

3.25a	8.09-8.06 (m, 2H), 7.25-6.96 (m, 10H), 6.52 (d, 4H, J=7.0Hz), 6.16-6.13 (m, 2H), 4.46 (s, 4H)
3.25b	7.94-7.65 (m, 5H), 7.44-7.18 (m, 6H), 6.97 (d, 2H, J=8Hz), 6.70-6.67 (m, 1H), 4.58 (s, 1H), 2.21 (s, 1H)
3.25c	9.11 (s, 1H), 8.04-7.15 (m, 12H), 2.39 (s, 3H)
3.32a	8.05-7.95 (m, 2H), 7.49-6.91 (m, 15H), 4.60-4.40 (m, 2H)
3.32b	8.21-8.05 (m, 4H), 7.85 (d, 2H, J=8.3Hz), 7.46-7.15 (m, 11H), 4.73-4.61 (m, 1H), 4.46-4.36 (m, 1H)
3.32c	7.99-7.91 (m, 3H), 7.58 (d, 2H, J=8.3Hz), 7.38-6.98 (m, 8H), 3.34-3.06 (m, 2H), 1.43-1.04 (m, 12H), 0.80 (t, 3H, J=6.7Hz)
3.32d	8.02-7.93 (m, 3H), 7.63-7.60 (m, 2H), 7.41-7.35 (m, 2H), 7.25-7.00 (m, 6H), 3.36-3.11 (m, 2H), 1.49-1.10 (m, 4H), 0.768 (t, 3H, J=7Hz)
3.32e	8.32 (d, 2H, J=7.8Hz), 8.10-7.90 (m, 5H), 7.53-7.31 (m, 6H), 7.15 (t, 2H, J=6.7Hz), 6.87 (d, 3H, J=7.8Hz), 6.44 (s, 1H), 2.04 (s, 3H)
3.32f	8.34 (s, br, 2H), 8.19-8.02 (m, 4H), 7.62-7.50 (m, 4H), 7.42-7.23 (m, 3H), 5.88-5.76 (m, 2H), 1.47-1.35 (m, 1H), 0.98-0.86 (m, 6H)
3.32g	8.36 (d, 2H, J=8.5Hz), 8.08 (d, 2H, J=5.6Hz), 7.97 (t, 2H, J=5.6Hz) 7.97 (t, 2H, J=6.6Hz), 7.61-7.40 (m, 4H), 7.32-7.21 (m, 3H), 5.85 (d, 1H, J=6.6Hz), 5.68-5.54 (m, 1H), 0.80 (s, 9H)
3.32h	8.42-8.00 (m, 5H), 7.70-7.06 (m, 8H), 5.54 (s, 1H), 2.35-2.16 (m, 1H), 1.90-1.56 (m, 3H), 0.98-0.75 (m, 6H)
3.32i	8.12-7.86 (m, 3H), 7.76-7.55 (m, 2H), 7.40-7.28 (m, 2H), 7.21-7.00 (m, 4H), 6.95 (s, 1H), 6.77 (d, 1H, J=8.3Hz), 4.44 (s, 1H), 2.38-2.25 (m, 1H), 1.95-1.10 (m, 9H)
3.32j	8.34-8.00 (m, 4H), 7.80-7.46 (m, 3H), 7.37-7.01 (m, 6H), 5.40 (s, 1H), 2.29-1.61 (m, 8H)
3.32k	10.34 (s, 1H), 8.28 (s, 1H), 8.01 (d, 2H, J=7.6Hz), 7.80-7.55 (m, 5H), 7.41-7.14 (m, 10H)
3.32l	10.85 (s, 1H), 8.79 (s, 1H), 8.21-7.87 (m, 6H), 7.75-7.10 (m, 11H)
3.32m	8.78 (s, 1H), 8.04-7.94 (m, 3H), 7.84-7.77 (m, 2H), 7.68-7.60 (m, 2H), 7.44-7.17 (m, 10H)

Table 3.4 ^{13}C NMR data of adducts **3.25a-c** and **3.32a-m**

	Benzotriazole						Carbazole							
Compd	C_4	C_5	C_6	C_7	C_{3a}	C_{7a}	C_1	C_2	C_3	C_4	C_{4a}	C_{9a}	>CH	Electrophile
3.25a	120.2	124.4	127.7	110.3	146.4	132.6	---	---	---	---	---	---	85.5	132.4 130.3 128.2 128.1 42.4
3.25b	120.1	124.6	128.6	110.3	145.9	132.5	---	---	---	---	---	---	75.6	138.8 134.2 131.8 129.3 126.4 119.9 72.2 21.1
3.25c	120.1	124.9	128.6	110.6	146.2	132.3	---	---	---	---	---	---	71.8	184.7 146.0 130.6 129.8 128.9 21.7
3.32a	119.9	124.3	127.8	109.5	146.1	132.8	109.5	123.5	120.4	120.2	126.2	138.8	69.8	135.3 129.1 128.4 127.2 37.2
3.32b	119.5	124.5	127.9	110.3	145.3	132.3	110.0	122.7	120.5	120.1	126.2	138.7	67.7	134.7 131.5 130.9 35.6
3.32c	119.7	124.0	127.5	109.5	146.0	132.7	109.4	123.4	120.1	120.0	126.1	138.8	68.4	31.5 31.0 29.0 28.9 25.4 22.4 13.9
3.32d	119.8	124.1	127.6	109.6	146.1	132.7	109.4	123.5	120.4	120.1	126.2	138.8	68.4	30.9 27.6 22.1 13.6
3.32e	119.2	124.4	127.7	110.9	144.8	133.4	110.8	122.7	120.1	120.0	126.9	138.5	71.1	137.2 137.0 128.4 126.1 71.1 20.6
3.32f	119.1	124.3	127.6	110.9	144.8	133.4	110.9	123.0	120.4	120.3	126.4	138.8	70.1	71.8 28.8 20.4 14.8

Table 3.4 ^{13}C NMR data of adducts **3.25a-c** and **3.32a-m** (contd.)

	Benzotriazole						Carbazole							
Compd	C_4	C_5	C_6	C_7	C_{3a}	C_{7a}	C_1	C_2	C_3	C_4	C_{4a}	C_{9a}	>CH	Electrophile
3.32g	119.0	123.9	127.3	110.9	144.6	133.2	110.7	123.0	120.2	120.1	126.1	138.7	69.3	73.7 35.7 26.1
3.32h			a											
3.32i			b											
3.32j			c											
3.32k	119.3	124.2	128.0	110.7	144.4	133.9	111.5	123.6	120.6	120.3	126.1	139.1	72.7	191.0 140.0 128.7 126.8
3.32l	119.4	124.5	128.1	110.6	144.9	133.3	111.0	123.5	120.4	120.3	126.2	139.7	67.6	162.0 138.1 128.9 128.3 124.5
3.32m	120.1	124.2	128.1	110.4	146.3	134.8	110.1	124.1	121.3	120.6	126.7	139.3	71.2	188.9 133.4 132.4 129.1 128.3

[a] Mixture of isomers: 144.1 141.4 139.5 133.3 128.1 127.9 126.2 125.4 124.4 120.3 120.1 119.3 114.5 110.6 110.4 78.47 72.36 28.58 27.53 7.91 7.45.

[b] Mixture of isomers: 145.0 141.2 138.6 133.8 128.7 126.4 126.3 124.9 124.0 123.7 120.9 120.6 120.5 120.4 120.2 119.9 113.1 109.5 108.6 77.0 75.3 36.5 34.3 25.6 21.3 21.1.

[c] Mixture of isomers: 144.5 141.0 138.9 133.2 127.7 126.3 125.3 124.3 120.0 119.9 119.6 119.3 113.6 110.2 110.1 84.9 73.4 38.1 37.9 23.4 23.0.

Table 3.5 Preparation of 2,4-dinitrophenylhydrazones **3.36a-l**

Compd	E	Method	Yield (%)	mp (°C)	Lit. mp (°C)
3.36a	$PhCH_2$-	A	78	134-136	120-121[a]
3.36b	4-$BrC_6H_4CH_2$-	B	81	153-154	----
3.36c	*n*-C_8H_{17}-	A	67	103-104	106[b]
3.36d	*n*-C_4H_9-	B	83	107-108	102-104[c]
3.36e	4-$MeC_6H_4CH(OH)$-	B	42	178-179	----
3.36f	$(CH_3)_2CHCH(OH)$-	B	76	131-132	----
3.36g	$(CH_3)_3CCH(OH)$-	B	71	155-156	----
3.36h	$(C_2H_5)_2C(OH)$-	B	73	182-184	----
3.36i	$(CH_2)_5C(OH)$-	B	71	171-172	217-218[d]
3.36j	$(CH_2)_4C(OH)$-	B	61	182-184	----
3.36k	PhNHC(=S)-	B	70	247-249	----
3.36l	PhNHC(=O)-	A	68	266-268	----

[a] Meyers, A. I.; Collington, E. W. *J. Am. Chem. Soc.* **1970**, *92*, 6676. [b] Malone, C. R.; Meyers, A. I. *J. Org. Chem.* **1974**, *39*, 623. [c, d] Meyers, A. I.; Nabeya, A. *J. Org. Chem.* **1973**, *38*, 36.

Table 3.6 Microanalyses data of 2,4-dinitrophenylhydrazones **3.36a-l**

Compd	Molecular formula	C	H	N	C	H	N
		Required (%)			Found (%)		
3.36a	$C_{14}H_{12}N_4O_4$	56.00	4.00	18.67	55.72	3.92	18.59
3.36b	$C_{14}H_{12}N_4O_4$	44.15	2.92	14.78	43.84	2.79	14.71
3.36c	$C_{15}H_{22}N_4O_4$	55.89	6.88	17.38	56.19	6.95	17.47
3.36d	$C_{11}H_{14}N_4O_4$	---	---	---	---	---	---
3.36e	$C_{15}H_{14}N_4O_5$	54.55	4.27	16.96	54.83	4.17	17.19
3.36f	$C_{11}H_{14}N_4O_5$	46.81	5.00	19.95	46.85	4.97	20.13
3.36g	$C_{12}H_{16}N_4O_5$	48.65	5.41	18.92	48.81	5.55	19.19
3.36h	$C_{12}H_{16}N_4O_5$	48.65	5.41	18.92	48.72	5.44	19.20
3.36i	$C_{13}H_{16}N_4O_5$	50.65	5.23	18.17	50.65	5.24	18.35
3.36j	$C_{12}H_{14}N_4O_5$	48.58	4.80	19.04	48.26	4.70	19.17
3.36k	$C_{14}H_{11}N_5O_4S$	48.69	3.21	20.28	48.48	3.21	20.64
3.36l	$C_{14}H_{11}N_5O_5$	51.07	3.37	21.27	51.02	3.24	21.39

Table 3.7 ^{1}H NMR data of 2,4-dinitrophenylhydrazones **3.36a-l**

3.36a	11.04 (s, 1H), 9.07 (d, 1H, J=3.5Hz), 8.31-8.27 (m, 1H), 7.96 (d, 1H, J=9.6Hz), 7.60 (t, 1H, J=5.9Hz)
3.36b	11.43 (s, 1H), 8.84 (s, 1H), 8.33 (d, 1H, J=6.6Hz), 7.86 (d, 1H, J=9.7Hz), 7.52 (d, 2H, J=6.4Hz), 7.26 (d, 2H, 6.6Hz), 3.69 (d, 2H, J=6.5Hz)
3.36c	11.02 (s, 1H), 9.11 (s, 1H), 8.35-8.21 (m, 1H), 7.92 (d, 1H, J=9.4Hz), 7.54 (t, 1H, J=5.5Hz), 2.50-2.35 (m, 2H), 1.61-1.60 (m, 16H), 0.95-0.80 (m, 3H)
3.36d	11.02 (s, 1H), 9.1 (d, 1H, J=6.2Hz), 8.31-8.26 (m, 1H), 7.97-7.9 (m, 1H), 7.57 (t, 1H, J=5.4Hz), 2.48-2.41 (m, 2H), 1.64-1.4 (m, 4H), 1.0-0.95 (m, 3H)
3.36e	11.41 (s, 1H), 8.85 (s, 1H), 8.41-8.35 (m, 1H), 8.10 (d, 1H), 7.35-7.15 (m, 4H), 6.05 (d, 1H), 5.30-5.20 (m, 1H), 5.30-5.20 (m, 1H), 2.30 (s, 3H)
3.36f	11.24 (s, 1H), 9.03 (d, 1H, J=2.6Hz), 8.28 (d, 1H, J=2.6Hz), 8.12 (d, 1H, J=2.6Hz), 8.12 (d, 1H, 9.7Hz), 7.76 (d, 1H, J=5.6Hz), 4.76 (d, 1H, J=4.8Hz), 4.11-4.02 (m, 1H), 2.01-1.89 (m, 1H), 1.04-0.98 (m, 6H)
3.36g	11.17 (s, 1H), 9.11 (t, 1H, J=2.1Hz), 8.33 (d, 1H, J=9.6Hz), 7.94 (d, 1H, J=9.6Hz), 7.71 (d, 1H, J=3.9Hz), 4.11 (s, 1H), 2.80 (s, 1H), 1.03 (s, 9H)
3.36h	11.40 (s, 1H), 8.83 (d, 1H, J=2.7Hz), 8.33 (q, 1H, J=2.7Hz), 7.97-7.94 (m, 2H), 4.86 (s, 1H), 1.73-1.56 (m, 4H), 0.95-0.84 (m, 6H)
3.36i	11.32 (s, 1H), 8.22 (d, 1H, J=2.6Hz), 8.34 (q, 1H, J=2.6Hz), 7.98 (s, 1H), 7.88 (d, 1H, J=5.7Hz), 4.99 (s, 1H), 1.78-1.24 (m, 10H)
3.36j	11.25 (s, 1H), 8.99 (d, 1H, J=2.6Hz), 8.29-8.25 (m, 1H), 8.02-7.97 (m, 2H), 4.81 (s, 1H), 2.05-1.66 (m, 8H)
3.36k	11.86 (s, 1H), 10.26 (s, 1H), 8.86 (d, 1H, J=2.4Hz), 8.52-8.35 (m, 2H), 8.10 (s, 1H), 7.85-7.73 (m, 2H), 7.55-7.31 (m, 2H), 7.20-2.13 (m, 1H)
3.36l	10.97 (s, 1H), 8.88 (s, 1H), 8.47-8.43 (m, 1H), 8.18-8.05 (m, 2H), 7.52-7.35 (m, 4H), 7.26-7.15 (m, 1H)

Table 3.8 ^{13}C NMR data of 2,4-dinitrophenylhydrazones **3.36a-l**

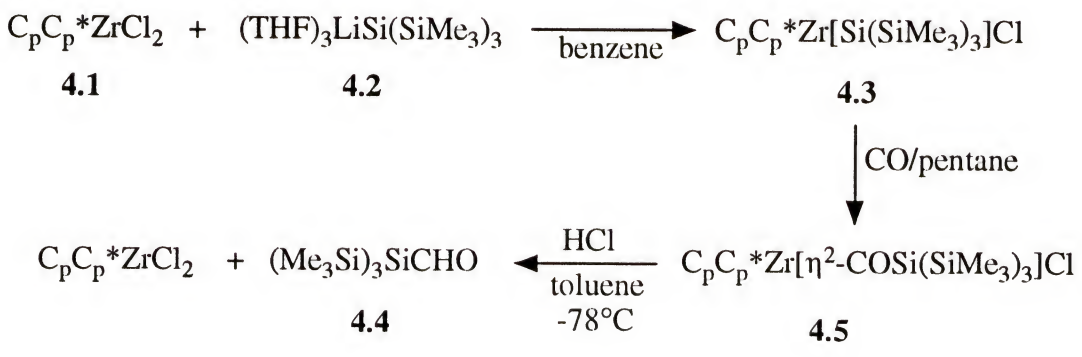
Compd	E	-C=N	2,4-DNP
3.36a	135.4 128.9 127.2 40.0	150.4	145.0 137.8 129.9 128.9 123.3 116.5
3.36b	135.9 131.3 131.0 119.8 37.7	152.2	144.7 136.6 129.5 128.7 122.8 116.3
3.36c	32.5 31.8 29.3 29.1 26.3 22.6 14.1	152.8	145.1 137.7 129.9 128.8 123.5 116.5
3.36d	32.2 28.3 22.2 13.8	152.8	145.1 137.6 129.9 128.7 123.4 116.5
3.36e	138.2 136.7 129.0 126.3 72.4 20.7	154.7	144.9 136.8 129.7 128.9 122.9 116.5
3.36f	74.7 32.0 17.5 17.0	153.4	144.4 136.7 128.8 128.1 122.3 116.3
3.36g	78.4 35.8 25.6	151.2	144.8 138.3 130.1 129.3 123.4 116.3
3.36h	74.5 30.4 7.7	158.4	145.0 136.6 129.6 128.9 122.9 116.6
3.36i	70.6 35.1 25.2 21.3	158.9	145.0 136.6 129.7 129.0 122.9 116.4
3.36j	79.7 37.3 22.5	156.1	144.0 136.0 128.3 127.6 121.9 115.6
3.36k	161.0 138.7 129.5 124.7 124.0 122.5	144.0	141.7 138.2 128.7 128.6 120.4 118.1
3.36l	a		

[a] Solubility too low to run carbon spectrum.

CHAPTER IV
SYNTHESIS OF FORMYLSILANES VIA (BENZOTRIAZOL-1-YL)(CARBAZOL-9-YL)METHANE AS A FORMYL ANION EQUIVALENT

4.1 Introduction

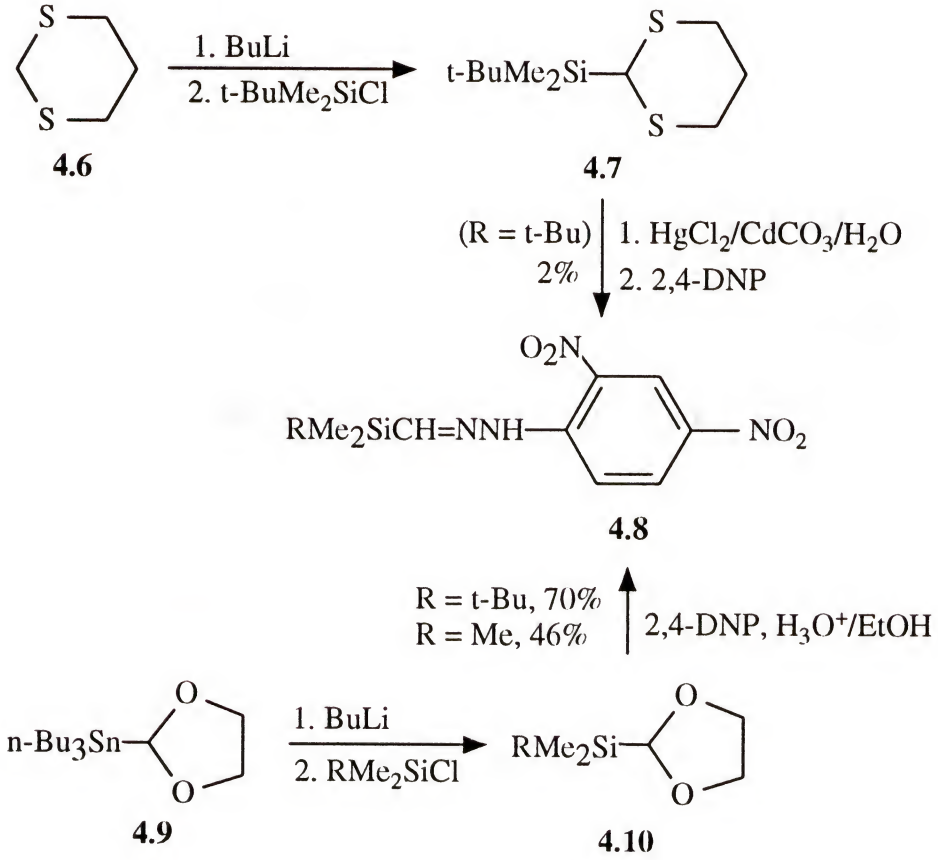
Acylsilanes have drawn a great attention in the last decade due to their interesting reactivities and diverse usefulness in organic synthesis [82CSR493, 89S179, 89S647, 92JOC7010]. A variety of methods have been developed for their synthesis and have been thoroughly reviewed [89S647]. Although early reports [54JA1613] indicated hydrolytic instability for an organosilicon structure having a carbonyl group directly bound to silicon, acylsilanes have been shown to be fairly stable. On the other hand, the chemistry of formylsilanes has remained virtually unexplored due to their high instability. In fact, only four formylsilanes have so far been reported although no less than three methods [88JA313, 92JA10078, 92JOC6617] were used. Tilly, T. D. *et al* reported [88JA313] that treatment of Zirconium η^2-silaacyl complex **4.5** with anhydrous HCl gas in toluene gave formyltris(trimethylsilyl)silane **4.4** in 55% yield (Scheme 4.1)



4.1 **4.2** **4.3** **4.4** **4.5**

Scheme 4.1

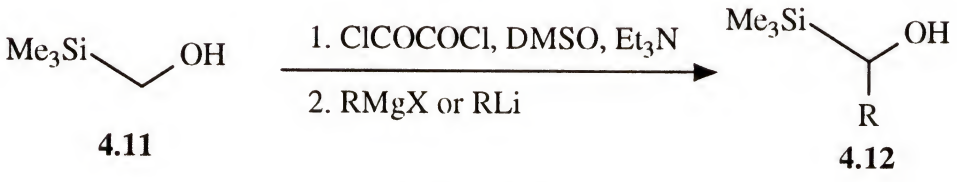
The synthesis of formyltriisopropylsilane was recently achieved by Soderquist, J. A. *et al* [92JA10078] *via* a modified three-step dithiane method. Thus, treatment of 1,3-dithiane with butyllithium followed by triisopropylsilyl chloride yielded 2-triisopropylsilyldithiane. This was then treated with $HgCl_2/HgO$ in methanol affording the dimethyl acetal of formyltriisopropylsilane which was hydrolyzed to give formyltriisopropylsilane in a good overall yield. Although formyltris(trimethylsilyl)silane and formyltriisopropylsilane have been found to be thermally stable, they are extremely sensitive to air, as evidenced by the fact that both decompose violently upon exposure to atmospheric oxygen (even ignite spontanously for $(Pr^i)_3SiCHO$). The instability of formylsilanes is further reflected in the high



Scheme 4.2

sensitivity of their synthetic yields to reaction conditions. Direct conversion of 2-triisopropyldithiane to formyltriisopropylsilane even under the mild Vedejs-Fuchs hydrolysis conditions [71JOC366] resulted in only 47% yield (GC). Silverman, R. B. *et al* [92JOC6617] found that hydrolysis of 2-*t*-butyldimethylsilyldithiane **4.7** under normal dithiane hydrolysis conditions gave formyl-*t*-butyldimethylsilane in only 2% yield while 70% yield was obtained when 2-*t*-butyldimethylsilyldioxolane **4.10** was hydrolyzed under mild acidic conditions (isolated as its 2,4-dinitrophenylhydrazone in both cases) (Scheme 4.2).

Other examples indicating the existence of formylsilanes were reported by Ireland, R. E. *et al* [85JOC2199] and Linderman, R. J. *et al* [88JOC1569] who carried out the Swern oxidation of (trimethylsilyl)methanol and isolated the products of nucleophilic attack on the presumably formed formyltrimethylsilane (Me_3SiCHO) (Scheme 4.3).



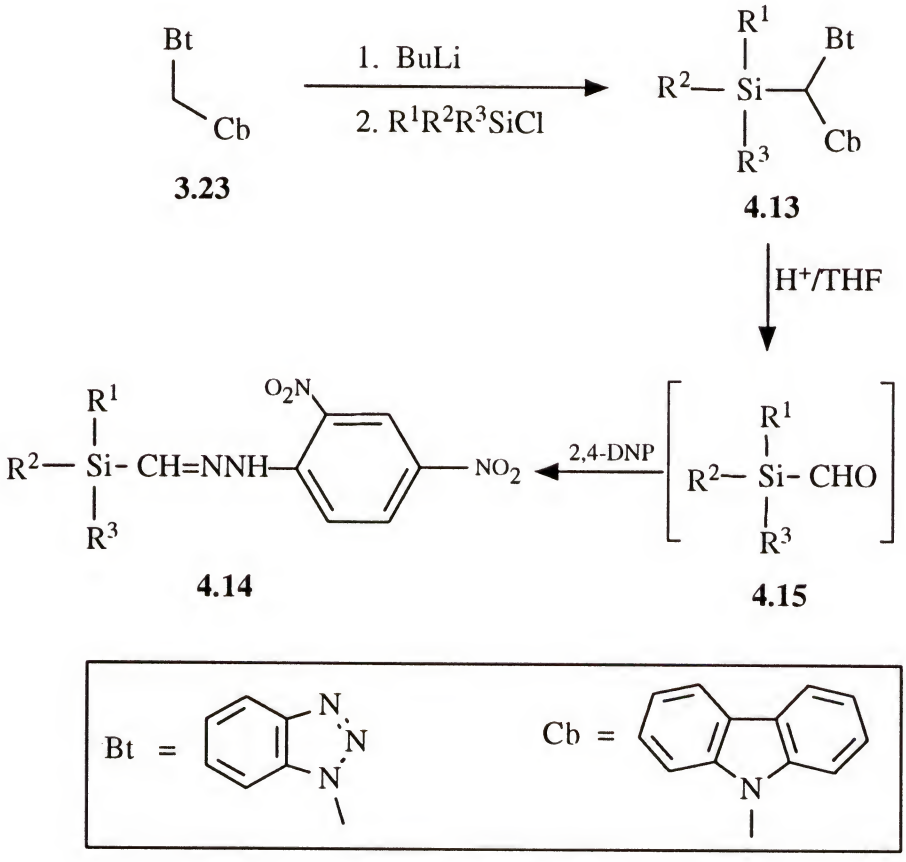
4.11 **4.12**

Scheme 4.3

Due to the high instability of formylsilanes, most of the methods used for the preparation of acylsilanes are not applicable to their synthesis. Even the relatively mild formyl anion methodology, such as 1,3-dithiane system, suffers low yields in the hydrolysis step.

4.2 Results and Discussion

We have demonstrated [91JOC2143, 91JOC6197, 93JOC1970] the use of (benzotriazol-1-yl)(carbazol-9-yl)methane **3.23** as a versatile formyl anion equivalent. The convenient reactivity of the anion of **3.23** towards a wide spectrum of electrophiles and the mild acidic conditions used for the hydrolysis of the intermediate products have prompted us to investigate the possibility of this system in the synthesis of formylsilanes.



3.23 **4.13** **4.14** **4.15**

Scheme 4.4

Thus, treatment of **3.23** with butyllithium at -78°C for 2 h followed by silyl chlorides, afforded the corresponding silylated products **4.13a-e** in excellent yields (Scheme 4.4 and Table 4.1). The insensitivity of the reaction to steric and/or electronic (alkyl or aryl) effects of the substituents in the silyl chlorides was testimony to the generality of this reaction. Another advantage of this reaction was that the crude products obtained were virtually pure (TLC and NMR) and could be used for the subsequent hydrolysis without further purification. Compounds **4.13a-e** were characterized by ^{1}H and ^{13}C NMR spectroscopy and their elemental analysis data.

Hydrolysis of the intermediate products **4.13a-e** was carried out in dilute sulfuric acid in the presence of 2,4-dinitrophenylhydrazine. In the cases of **4.13a-d**, the reactions went to completion at room temperature within 24h and afforded the 2,4-dinitrophenylhydrazones of the corresponding formylsilanes **4.14a-d** (Scheme 4.4 and Table 4.2). The low yield of **4.14a** was presumably attributed to the much lower stability of free formyltrimethylsilane. Attempts to hydrolyze compound **4.13e** under similar conditions resulted in recovery of most of the starting material. The electron withdrawing nature of the phenyl group, which disfavored the formation of the intermediate imminum ion (for hydrolysis mechanism see Chapter III, Scheme 3.5), was believed to be responsible for this behavior. However, when the hydrolysis was carried out at 55-60°C, the 2,4-dinitrophenylhydrazone of formyltriphenylsilane **4.14e** was obtained in a yield of 58%. To assess the stability of formylsilanes, such as formyltriisopropylsilane, compound **4.13c** was subjected to the same hydrolysis conditions as described above for **4.13a-d** except that 2,4-dinitrophenylhydrazine was not initially added in the reaction mixture. After **4.13c** was completely consumed (as indicated by TLC), 2,4-dinitrophenylhydrazine was added and the mixture stirred at room temperature for an additional 4h. In this case, the 2,4-dinitrophenylhydrazone of

formyltriisopropylsilane was obtained in only 41% yield, indicating the partial decomposition of formyltriisopropylsilane under these conditions.

In conclusion, we have developed a novel approach to the synthesis of different substituted formylsilanes by using (benzotriazol-1-yl)(carbazol-1-yl)methane as a formyl anion equivalent. The present method is advantageous in terms of simplicity and generality as demonstrated by the good overall yields and the diversity of silyl chlorides that can be used. The mild hydrolysis conditions avoid the use of toxic reagents and allow a wide range of formylsilanes to be readily accessible.

Table 4.1 Preparation of Intermediate Products **4.13a-e**

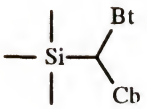
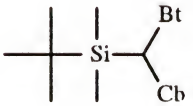
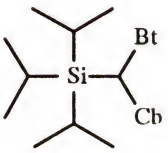
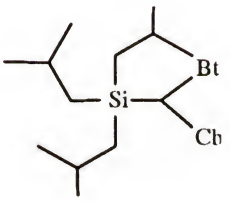
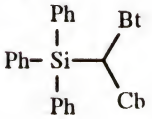
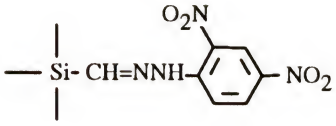
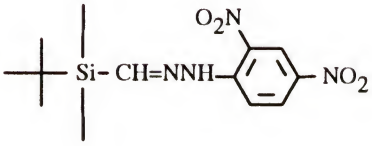
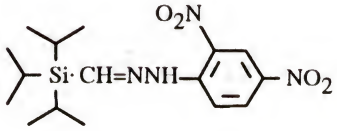
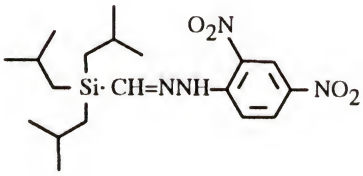
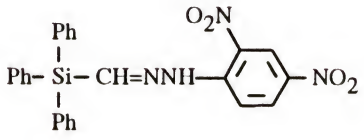
Entry	Compound	Yield (%)	M.P. (°C)	Recryst. solvent	Molecular formula
4.13a		91	185-186	methanol	$C_{22}H_{22}N_4Si$
4.13b		89	166-168	hexane	$C_{25}H_{28}N_4Si$
4.13c		92	130-131	hexane	$C_{28}H_{24}N_4Si$
4.13d		90	117-118	methanol	$C_{31}H_{40}N_4Si$
4.13e		95	237-238	methanol	$C_{37}H_{28}N_4Si$

Table 4.2 Preparation of 2,4-Dinitrophenylhydrazones **4.14a-e**

Entry	Compound	Yield (%)	M.P. (°C)	Lit. M.P. (°C)
4.14a		48	135-136	141-142[a]
4.14b		81	137-138	139-140[a]
4.14c		79	111-112	109-111[b]
4.14d		84	145-146	--
4.14e		58	173-174	--

[a] Ref. [92JOC6617]. [b] Ref. [92JA10078].

4.3 Experimental

Melting points were determined on a bristoline hot-stage microscope and are uncorrected. ^1H (300 MHz) NMR spectra were recorded on a Varian VXR-300 (FT

mode) spectrometer with Me_4Si as internal standard. ^{13}C NMR spectra were recorded at 75 MHz on the same instrument using solvent peaks ($CDCl_3$, δ 77.0 or DMSO-d_6, δ 39.5) as references. Elemental analyses (CHN) were carried out using a Carlo Erba 1106 elemental analyzer. Tetrahydrofuran (THF) was freshly distilled from sodium-benzophenone. All moisture sensitive reactions were carried out in a dry argon atmosphere.

The following compound was prepared by a known literature procedure: (benzotriazol-1-yl)(carbazol-9yl)methane **3.23**, mp 193-5°C, lit. [91JOC2143] mp 193-5°C.

4.4.1 Lithiation of (benzotriazol-1-yl)(carbazol-9-yl)methane and reaction with electrophiles. General procedure

n-BuLi (2.5M in hexane; 4.4 mL, 11 mmol) was added to a solution of (benzotriazol-1-yl)(carbazol-9-yl)methane (2.98 g, 10 mmol) in dry THF (80 mL) at -78°C. The solution was stirred at -78°C for 2 h and then an appropriate silyl chloride (11 mmol) in THF (10 mL) was added. The mixture was stirred at -78°C for 4 h and then at room temperature for 12 h. The reaction mixture was poured into saturated aqueous NH_4Cl (40 mL), and the aqueous layer extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with water (1 x 25 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to afford the crude products which were then purified to give analytically pure products (Table 4.1).

(Benzotriazol-1-yl)(carbazol-9-yl)(trimethylsilyl)methane **4.13a**. ^1H NMR ($CDCl_3$): 8.58-7.92 (m, 4H), 7.85-7.50 (m, 2H), 7.45-6.95 (m, 7H), 0.35 (s, 9H). ^{13}C NMR ($CDCl_3$): 145.2, 139.5, 133.0, 132.1, 127.9, 127.8, 126.2, 124.4, 124.3, 122.8,

120.44, 120.38, 120.32, 119.6, 119.5, 119.4, 110.5, 110.12, 110.06, 60.2, 1.8. *Analysis* ($C_{22}H_{22}N_4Si$): calcd: C 71.32 H 5.99 N 15.13; found: C 71.22 H 5.99 N 15.08.

(Benzotriazol-1-yl)(*t*-butyldimethylsilyl)(carbazol-yl)methane **4.13b**. ^1H NMR ($CDCl_3$): 8.10 (d, 1H, J=7.8Hz), 7.99 (d, 2H, J=1.09Hz), 7.78 (d, 1H, J=8.3Hz), 7.67-7.60 (m, 2H), 7.34-7.10 (m, 6H), 6.95 (s, 1H), 0.89 (s, 9H), 0.71 (s, 3H), 0.0 (s, 3H). ^{13}C NMR ($CDCl_3$): 145.8, 140.2, 139.2, 133.4, 127.8, 126.2, 125.8, 124.2, 123.6, 123.1, 120.9, 119.99, 119.92, 119.8, 111.9, 109.6, 107.8, 58.0, 27.0, 17.4, -2.6. *Analysis* ($C_{25}H_{28}N_4Si$): calcd: C 72.77 H 6.84 N 13.58; found: C 72.63 H 6.86 N 13.56.

(Benzotriazol-1-yl)(carbazol-9-yl)(triisopropylsilyl)methane **4.13c**. ^1H NMR ($CDCl_3$): 8.09 (d, 1H, J=7.81Hz), 7.96 (d, 2H, J=8.10Hz), 7.85 (d, 1H, J=8.3Hz), 7.74-7.50 (m, 2H), 7.42-7.10 (m, 6H), 7.09 (s, 1H), 1.61 (m, 3H), 1.04 (d, 9H, J=7.3Hz), 1.02 (d, 9H, J=6.5Hz). ^{13}C NMR ($CDCl_3$): 145.9, 140.3, 139.3, 133.1, 127.8, 126.0, 125.7, 124.2, 123.6, 123.3, 120.8, 119.97, 119.85, 119.80, 111.7, 109.7, 108.2, 58.0, 18.8, 18.6, 12.2. *Analysis* ($C_{28}H_{34}N_4Si$): calcd: C 73.97 H 7.54 N 12.33; found: C 74.09 H 7.53 N 12.32.

(Benzotriazol-1-yl)(carbazol-9-yl)(triisobutylsilyl)methane **4.13d**. ^1H NMR ($CDCl_3$): 8.15-7.88 (m, 3H), 7.80-7.50 (m, 2H), 7.42-6.91 (m, 7H), 6.89 (s, 1H), 1.87-1.69 (m, 3H), 1.03 (m, AB system, 6H), 0.89 (d, 9H, J=6.5Hz), 0.75 (d, 9H, J=6.6Hz). *Analysis* ($C_{31}H_{40}N_4Si$): calcd: C 74.95 H 8.12 N 11.28; found: C 75.14 H 8.20 N 11.33.

(Benzotriazol-1-yl)(carbazol-9-yl)(triphenylsilyl)methane **4.13e**. ^1H NMR ($CDCl_3$): 8.08-7.89 (m, 4H), 7.60-7.48 (m, 8H), 7.46-7.30 (m, 4H), 7.29-7.05 (m, 10H), 6.98-6.92 (m, 2H). ^{13}C NMR ($CDCl_3$): 145.9, 136.6, 132.9, 131.3, 130.2, 127.9, 127.8, 124.3, 120.0, 119.8, 109.7, 60.4. *Analysis* ($C_{37}H_{28}N_4Si$): calcd: C 79.83 H 5.07 N 10.07; found: C 79.98 H 5.07 N 10.07.

4.3.2 Synthesis of 2,4-Dinitrophenylhydrazones **4.14a-e.** General Procedure

An appropriate intermediate product **4.13** (2 mmol) was added to a solution of 2,4-dinitrophenylhydrazine (2.4 mmol) in tetrahydrofuran (20 ml), water (10 ml) and conc. H_2SO_4 (1 ml). The mixture was stirred at room temperature (for **4.13e**, 55-60°C) for 24 h under nitrogen and extracted with chloroform (3 x 30 ml). The combined organic layers were washed with water (3 x 20 ml), dried over $MgSO_4$ and evaporated to give a residue which was triturated with chloroform (15 ml) and kept at -15°C for 5 h. The crystallized carbazole was filtered off and the filtrate evaporated at reduced pressure to give the crude product which was recrystallized from ethanol to afford the pure product (Table 4.2).

2,4-Dinitrophenylhydrazone of formyltrimethylsilane **4.14a**. ^{1}H NMR ($CDCl_3$): 11.05 (s, 1H), 9.07 (d, 1H, J=2.5Hz), 8.29 (dd, 1H, J_1=9.6Hz and J_2=2.5Hz), 8.02 (d, 1H, J=9.6Hz), 7.84 (s, 1H), 0.30 (s, 9H). ^{13}C NMR ($CDCl_3$): 160.1, 144.7, 138.0, 129.7, 128.8, 123.2, 116.8, -2.5. *Analysis* ($C_{10}H_{14}N_4O_4Si$): calcd: C 42.54 H 5.00 N 19.84; found: C 42.91 H 4.94 N 20.12.

2,4-Dinitrophenylhydrazone of formyl-*t*-butyldimethylsilane **4.14b**. ^{1}H NMR ($CDCl_3$): 11.09 (s, 1H), 9.10 (d, 1H, J=2.4Hz), 8.32 (dd, 1H, J_1=9.5Hz and J_2=2.4Hz), 8.02 (d, 1H, J=9.5Hz), 7.85 (s, 1H), 1.00 (s, 9H), 0.25 (s, 2H). ^{13}C NMR ($CDCl_3$): 158.6, 144.7, 138.2, 129.8, 128.8, 123.2, 116.9, 26.3, 16.7, -6.7. *Analysis* ($C_{13}H_{20}N_4O_4Si$): calcd: C 48.13 H 6.21 N 17.27; found: C 47.91 H 6.17 N 17.22.

2,4-Dinitrophenylhydrazone of formyltriisopropylsilane **4.14c**. ^{1}H NMR ($CDCl_3$): 11.10 (s, 1H), 9.13 (d, 1H, J=2.5Hz), 8.35 (dd, 1H, J_1=9.7Hz and J_2=2.5Hz), 8.00 (d, 1H, J=9.7Hz), 7.84 (s, 1H), 1.38-1.22 (m, 3H), 1.46 (d, 18H, J=7.0Hz). ^{13}C NMR ($CDCl_3$): 157.3, 144.7, 138.2, 130.0, 128.9, 123.4, 116.9, 18.5, 10.8. *Analysis* ($C_{16}H_{26}N_4O_4Si$): calcd: C 52.44 H 7.15 N 15.29; found: C 52.37 H 7.13 N 15.37.

2,4-Dinitrophenylhydrazone of formyltriisobutylsilane **4.14d**. ^{1}H NMR ($CDCl_3$): 11.06 (s, 1H), 9.13 (d, 1H, J=2.5Hz), 8.34 (dd, 1H, J_1=9.5Hz and J_2=2.5Hz), 8.00 (d, 1H, J=9.5Hz), 7.83 (s, 1H), 1.96-1.82 (m, 3H), 0.98 (d, 18H, J=6.5Hz), 0.83 (d, 6H, J=7.0Hz). ^{13}C NMR ($CDCl_3$): 159.9, 144.8, 138.2, 130.0, 128.9, 123.4, 116.9, 26.5, 24.8, 23.4. *Analysis* ($C_{19}H_{32}N_4O_4Si$): calcd: C 55.86 H 7.89 N 13.71; found: C 55.95 H 7.88 N 13.56.

2,4-Dinitrophenylhydrazone of formyltriphenylsilane **4.14e**. ^{1}H NMR ($CDCl_3$): 11.29 (s, 1H), 9.07 (d, 1H, J=2.5Hz), 8.28-8.20 (m, 2H), 7.88 (d, 1H, J=9.5Hz), 7.68-7.58 (m, 6H), 7.57-7.36 (m, 9H). ^{13}C NMR ($CDCl_3$): 154.8, 144.6, 138.6, 136.0, 131.7, 130.3, 129.9, 129.2, 128.2, 123.1, 117.1. *Analysis* ($C_{25}H_{20}N_4O_4Si$): calcd: C 64.09 H 4.30 N 11.96; found: C 63.80 H 4.26 N 11.96.

CHAPTER V
SUBSTITUTED (BENZOTRIAZOL-1-YL)(CARBAZOL-9-YL)METHANES: NOVEL ACYL SYNTHON EQUIVALENTS

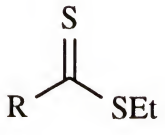
5.1 Introduction

Carbon atoms attached to two heteroatoms are versatile intermediates in synthetic organic chemistry. The greater electronegativity of these heteroatoms renders facile removal of the protons on the carbon atom allowing further functionalization and/or carbon-carbon bond formation. Hydrolytic removal of these heteroatoms forms carbonyl compounds. Thus compounds of type $XYHC^-$ are utilized as formyl anion equivalents, while $XYRC^-$ are potential acyl anion equivalents. In many cases, the parent precursor ($XYCH_2$) is the same for both these types of anion equivalents.

Acyl anion equivalents are of intense current interest: Sengupta and Snieckus [90JOC5680] have summarized recent references and the subject has been comprehensively reviewed [79AG(E)239; 79S633; 79OR1; 87MI1]. Among the more common acyl anion precursors where X = Y = S are 2-substituted 1,3-dithianes **5.1** [75JOC231; 82TL667; 84JA2949] (Scheme 5.1), thioester **5.2** [78TL4657], bis(arylthio)acetals **5.3** [79JCS(P1)1074; 80TL4763] and also oxidized thioacetals **5.4** [73TL3267; 76JOC3975]. In most cases, these precursors are treated with a strong base to generate the acyl anion equivalent which is then reacted with an electrophile, followed by removal of the heteroatom moiety. These systems are limited by the conditions required for initial deprotonation, by the reactivity of the anion and by the conditions needed for the final hydrolysis step. Whereas the anions of **5.1** and **5.4** react readily with electrophiles, conversion to the carbonyl compound requires complex

formation with a heavy metal cation (usually a mercury (II) salt [67JA431; 67JA434]) or making one of the sulfur atoms more electrophilic (for **5.1** through oxidation) [75JCS(P1)888]. Recently, electrolysis, involving anodic oxidation followed by nucleophilic attack with water [90TL2599] has been employed in cases where chemical transformations were unsuccessful. Alkylations of bis(alkylthio)acetals occur in low yields unless alternative approaches involving initial addition of a Grignard reagent to the dithioester **5.2** followed by reaction with an electrophile are used [77T2949]. Although the arylthio groups enhance the stabilization of the anion of **5.3**, compounds **5.3** have not found widespread applications due to the difficulty in alkylating the corresponding lithium derivatives. Thus, α,β-unsaturated ketones will

5.1



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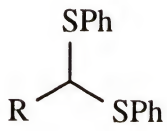

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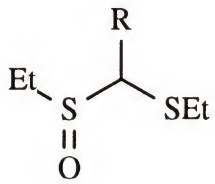
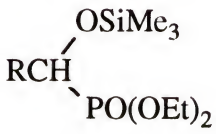


5.4



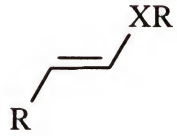
5.5

RCH_2NO_2

5.6

$^tBuNHN{=}CHR$

5.7



5.8a X = O
b X = S
c X = Se

Scheme 5.1

react only after formation of the cuprates [72JA8641] and with aldehydes and ketones the reaction occurs only in the presence of N,N,N',N'-tetramethylethylenediamine (TMEDA) [79JCS(P1)1074]. Furthermore, alkylations of **5.3** are possible only *via* treatment with butyllithium in hexane at 0°C in the presence of TMEDA [80TL4763].

In certain cases, organometallic reagents such as Grignard reagents, phenyllithium, or butyllithium have cleaved one of the phenylthio groups [63JOC961].

An example of an acyl anion precursor of type X ≠ Y ≠ S is the silyloxy phosphonate **5.5** which can be deprotonated and treated with electrophiles [78TL363; 79TL4475; 80TL1017; 80JOC3994]. Deprotonation, reaction with the electrophile and the subsequent hydrolysis to the ketone all occur in high yields. However, most of the examples deal with cases where R = phenyl. When R = alkyl [79TL4475], the electrophiles employed were alkyl and benzyl halides. Thus only simple ketones have been prepared by this route.

The ability of a nitro group to stabilize an α-carbanion has led to the use of primary nitroalkanes **5.6** for the synthesis of ketones [79HCA2258; 83TL647]; this is an example of an acyl anion precursor containing only one heteroatom-linked group. Primary nitroalkanes, on base catalyzed treatment with carbonyl compounds, afford the adducts in moderate yields [79HCA2258; 83TL647]. If additional activating groups are present at the β-position, an α,β-dideprotonated species is obtained with subsequent electrophilic addition occurring at the β-position [77TL1161]. These nitro derivatives can then be converted to the ketones by electrolysis [83S763], by the Nef reaction [74TL3215], by chromium [70JCS(C)1182], or persulfate [70JOC295] oxidation or by titanium (III) chloride [83TL647]. However, difficulties associated with simple C-alkylation have hindered exploitation of nitroalkanes in synthetic schemes.

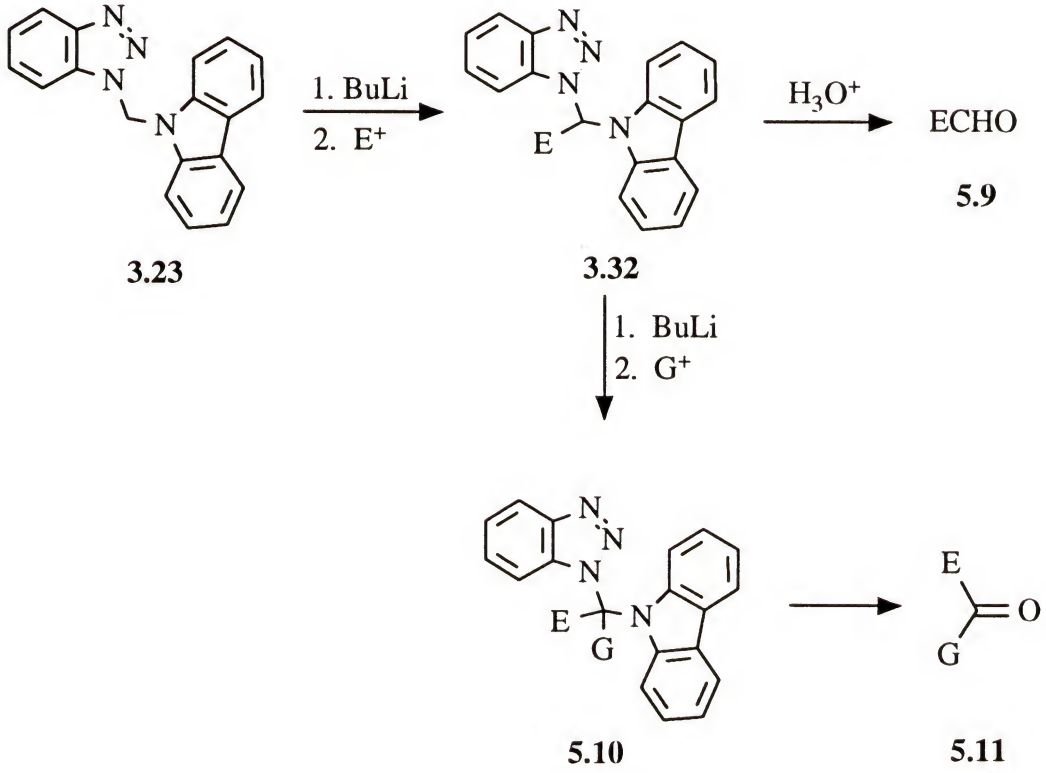
Other examples of this type are the *t*-butylhydrazone [83JCS(CC)1040] **5.7** (obtained by the reaction of an aldehyde and *t*-butylhydrazine), and vinyl compounds such as vinyl ethers **5.8a** [72LA208; 74JA7125], vinyl sulfides **5.8b** [73JA2694; 82CL593], and vinyl selenides **5.8c** [78AG(E)526; 78JOC3794]. Recently, Yamamoto *et al.* [90JOC4515] have developed a protected hydroxymalononitrile as an acyl anion

equivalent which has been employed in the preparation of masked activated esters but not ketones. The reaction of alkyl halides with the anion of **5.7** is slow (1-2 days). The initially formed azo intermediate tautomerises in trifluoroacetic acid to yield the ketone hydrazone. With carbonyl compounds as the electrophiles, the intermediate azo alcohol is unstable and requires further *in situ* treatment with butyllithium followed by a water quench to generate the α-hydroxyhydrazones in moderate yields. Hydrolysis of these intermediates is carried out in the presence of oxalic acid-water or phosphoric acid [83JCS(CC)1040].

Vinyl ethers **5.8a** (R = H) furnish anions on treatment with *t*-butyllithium which react with alkyl halides and carbonyl compounds in good yields. Acid hydrolysis then affords the methyl ketones [74JA7125]. For the vinyl sulfides **5.8b**, acyl anion equivalents where R = H are also known. Thus organometals such as *s*-butyllithium [73JA2694], LDA in THF/HMPA or LDA in hexanes [77JCS(CC)522] form the corresponding anions which then react with various electrophiles in good to moderate yields. The selective choice for the base and the solvent system is to prevent addition of the alkyllithium across the double bond [62JOC2698]. For the seleno ethers **5.8c**, both types of vinyl precursors (R = H and R = alkyl) are known. As in the previous case, carefully controlled conditions are required for proton abstraction. Alkylation occurs with LDA, while with butyllithium in tetrahydrofuran, or in diethyl ether, cleavage of the C-Se bond or addition across the double bond occurs [78AG(E)526]. When R = alkyl, the strongly basic mixture of potassium diisopropylamide-lithium *t*-butoxide (KDA) is required [78JOC3794]. The selenium is then usually removed by mercury reagents.

5.2 Results and Discussion

We have demonstrated [91JOC2143] that (benzotriazol-1-yl)(carbazol-9-yl)-methane **3.23** is a versatile formyl anion equivalent: its readily formed anion reacts with a variety of electrophiles to afford products **3.32** in good yields which on acid catalyzed hydrolysis afford the corresponding aldehydes. We have now found that the



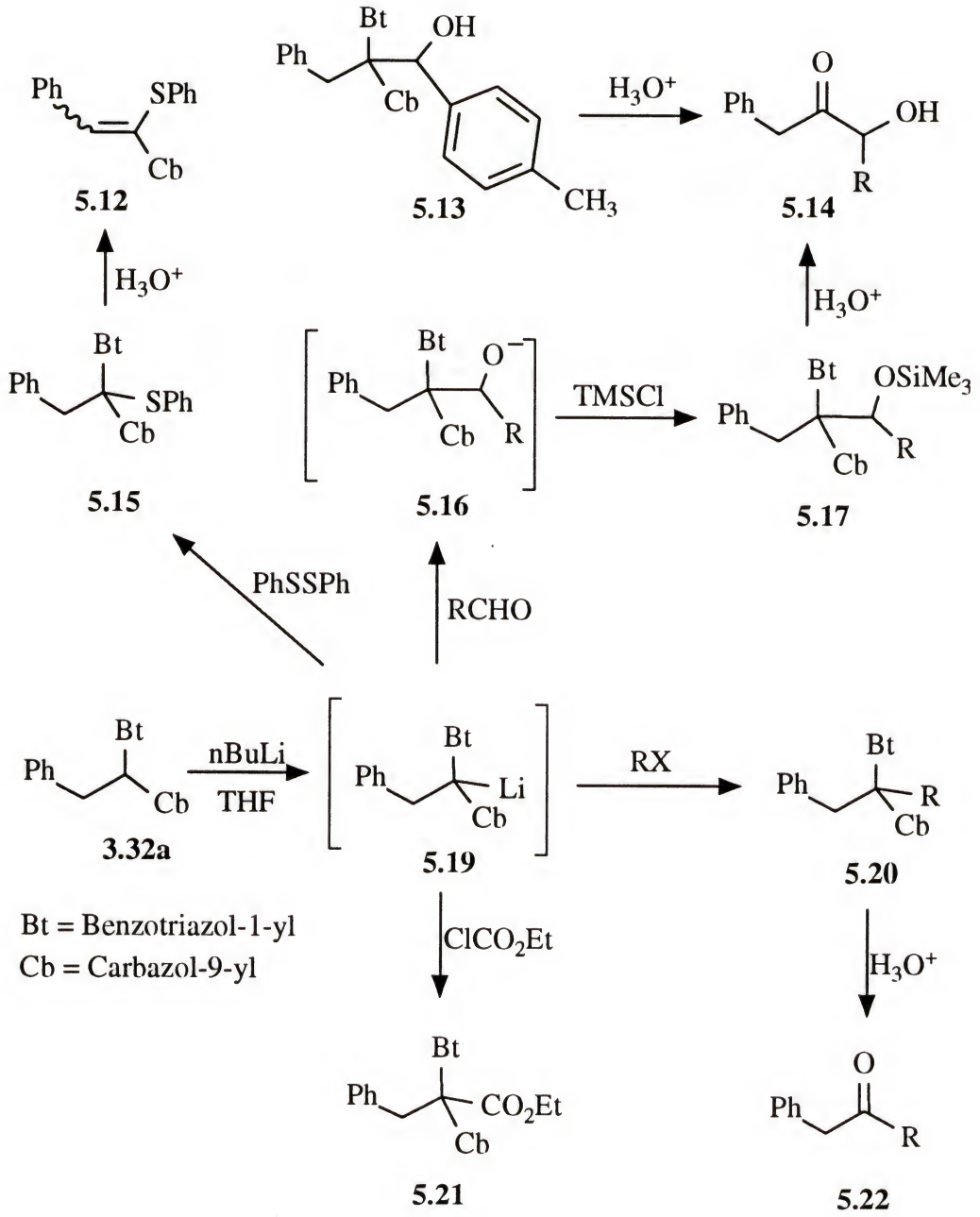
Scheme 5.2

intermediates of type **3.32** can themselves undergo deprotonation and that the resulting anions react with electrophiles to form the disubstituted derivatives **5.10** which upon mild acidic hydrolysis afford ketones **5.11**. Hence the compounds **3.32** are general acyl anion equivalents (Scheme 5.2).

5.2.1 Phenacetyl Anion Equivalent **5.19**

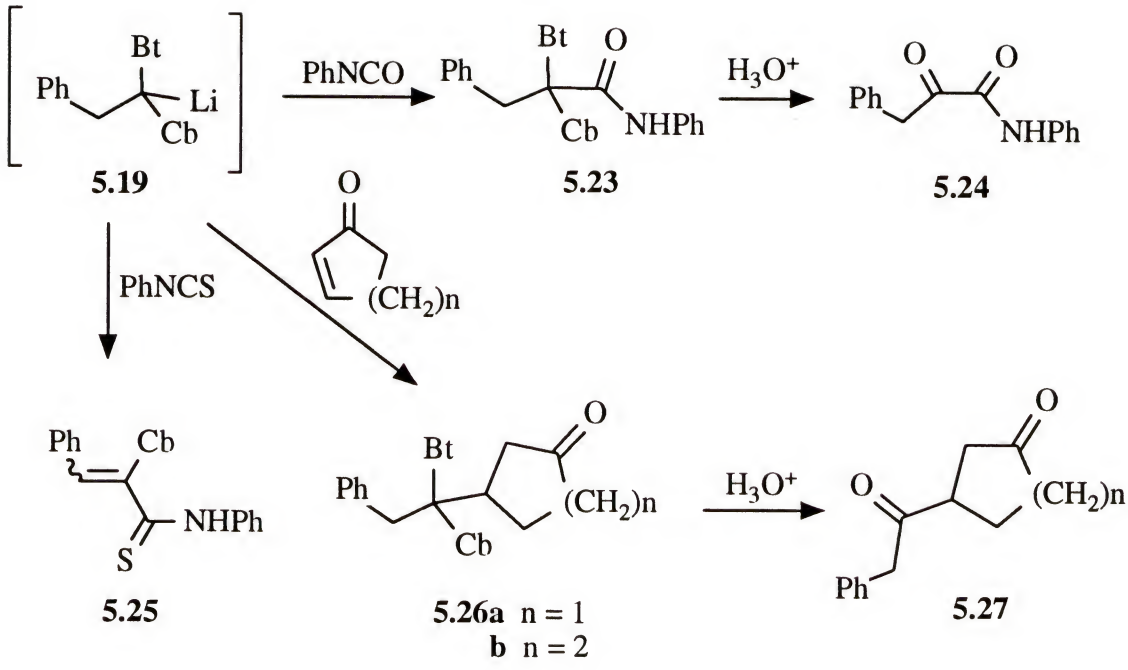
Our initial work was carried out with 1-(benzotriazol-1-yl)-1-(carbazol-9-yl)-2-phenylethane **3.32a** (Scheme 5.3), prepared from readily available (benzotriazol-1-yl)(carbazol-9-yl)methane [91JOC2143]. The benzyl derivative **3.32a** underwent deprotonation with butyllithium at -78 °C and anion **5.19** reacted with benzyl bromide, methyl iodide and butyl iodide to give the corresponding alkylated products **5.20a-c** (78-88%) (Schemes 5.3 and 5.4). Similar reactions of anion **5.19** with phenyl isocyanate, with diphenyl disulfide and with ethyl chloroformate proceeded smoothly and afforded the expected amide **5.23**, the phenylthio derivative **5.15** and the ester **5.21** (84-95%) (see Table 5.1).

Anion **5.19** also reacted with aldehydes to afford the expected secondary alcohol products. These compounds showed some tendency to revert back to the starting materials. However, good yield (85%) could be obtained with benzaldehyde provided the intermediate alcohol anion **5.16** was converted to its trimethylsilyl derivative **5.17** by addition of trimethylsilyl chloride to the reaction mixture prior to workup. With *p*-tolualdehyde, the alcohol **5.13** was obtained and was stable enough to be isolated without such addition.



Scheme 5.3

The structures of **5.13**, **5.15**, **5.17**, **5.20a-c**, **5.21** and **5.23** were confirmed by the ^{1}H and ^{13}C NMR spectra and by their CHN microanalyses data. Proton spectra are



Scheme 5.4

recorded in Table 5.3. The presence of the chiral center rendered the adjacent methylene protons of the benzyl group nonequivalent and they appeared as an AB pattern between 4 and 5 ppm. The difference in the chemical shifts for the two protons varied from 0.14 to 0.62 ppm. The aromatic signals were generally uninformative, but the signal patterns of the substituents and the integral ratios confirmed the structures of the products.

In the ^{13}C NMR spectra all the compounds showed the characteristic six peaks for the benzotriazole group, the six peaks for the carbazole group, the five peaks of the benzyl group, and the quarternary carbon which resonated between 82 and 91 ppm (Table 5.4). The remaining resonances were characteristic of the substituents introduced. Thus for the amide **5.23**, the carbonyl resonance was observed at about 164 ppm, while the carbonyl group for the ester **5.21** was found at 165.6 ppm.

It was noteworthy that anion **5.19** added regiospecifically 1,4 to the α,β-unsaturated ketone 2-cyclopentenone to yield **5.26a** (76%) as shown by its NMR spectra (Scheme 5.4). At room temperature, the ^{1}H NMR spectrum of the product displayed broad signals for the aliphatic protons indicating restricted rotation. However at 45 °C, the signals were sharp and the pattern indicated formation of **5.26a**. In addition to the expected signals for carbazole, benzotriazole and the benzyl group, the resonance at 214.1 ppm indicated that a carbonyl group was present. In the ^{1}H NMR spectrum, the absence of the vinylic protons, indicated that exclusive 1,4-addition had occurred. Similarly, 2-cyclohexenone afforded the corresponding 1,4-addition product **5.26b** (81%). The ketone resonance was observed at 208.7 ppm.

When the anion **5.19** was treated with phenyl isothiocyanate, the product isolated displayed no benzotriazole resonances in the NMR spectra. Furthermore, the absence of the AB pattern for the benzylic protons and of the corresponding carbon between 82 and 90 ppm in the ^{13}C NMR spectrum as well as the presence of a signal at 192 ppm, indicated that electrophilic addition with concomitant elimination of benzotriazole had occurred to afford the styryl derivative **5.25**. This was confirmed by the combustion analysis. Elimination of benzotriazole only occurred when the electrophile was phenyl isothiocyanate. With electrophiles such as isocyanates or aldehydes (cases where electrophilic addition also led to an anionic intermediate), only the normal products **5.23**, **5.13** and **5.17** were obtained.

We found that compounds **5.13**, **5.17**, **5.20a-c**, **5.23** and **5.26a,b** could easily be hydrolyzed under relatively mild conditions: treatment at 20 °C with tetrahydrofuran/0.9M aqueous hydrochloric acid solution showed the complete disappearance (TLC) of the starting material after 24 h and afforded the corresponding carbonyl derivatives in moderate to good yields. Isolation of the ketones was readily achieved by extracting the reaction mixture with hexane since carbazole and

benzotriazole were not soluble. The crude products thus obtained were purified by column chromatography.

In this way, the alkylated derivatives **5.20a-c** gave the corresponding simple ketones **5.22a-c** (63-82%). The product **5.23** from the phenyl isocyanate reaction afforded the α-ketoamide **5.24** (62%). The products **5.17** and **5.13** from aldehydes, gave α-hydroxyketones **5.14a,b** (51-57%). The 1,4-addition products yielded the γ-diketones **5.27a,b** (67-81%) (Table 5.5).

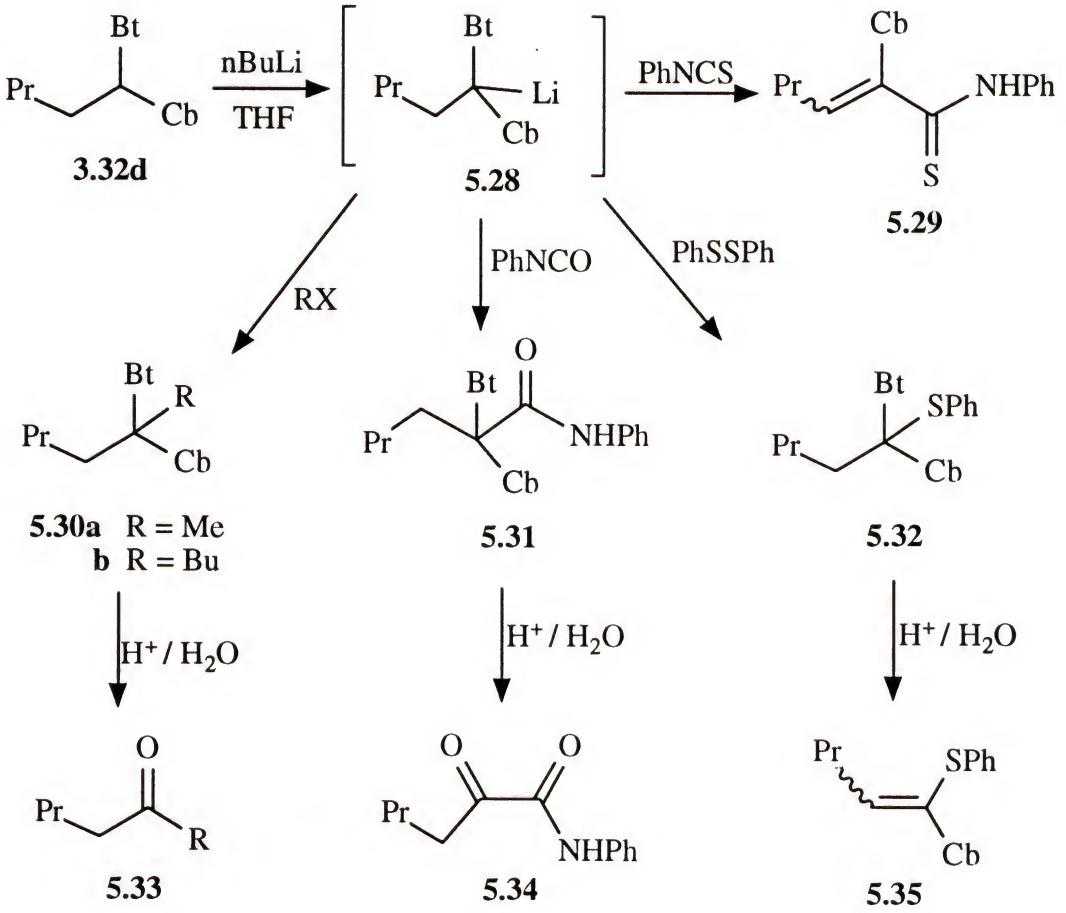
The ketone products were characterized by comparision with literature data or by elemental analysis/high resolution mass spectroscopy and by their NMR spectra (Tables 5.5-5.7). The ^{13}C NMR spectra of the ketones displayed the carbonyl resonance between 205 and 208 ppm except for the α-carboxamido derivative **5.24** where the keto carbon was observed at 196 ppm while the amido carbon was further upfield at 157 ppm.

When the phenylthio derivative **5.15** was subjected to hydrolysis, loss of benzotriazole was accompanied by formation of the styryl derivative **5.12** which was resistant to further hydrolysis. This was confirmed by the absence of the benzotriazole, benzylic and keto resonances in the ^{13}C NMR spectra of the products and correct combustion analyses for the postulated product.

5.2.2 Pentanoyl Anion Equivalent **5.28**

Similarly, the butyl analog **3.32d** reacted readily with butyllithium and the anion **5.28** was trapped with methyl iodide and butyl iodide to afford **5.30a** (91%) and **5.30b** (94%) respectively (Scheme 5.5). Reaction with phenyl isocyanate afforded the amide **5.31** (86%), and with diphenyl disulfide, the phenylthio derivative **5.32** (87%)

(Table 5.8). As in the phenacetyl case, reaction with phenyl isothiocyanate led to elimination of benzotriazole to give **5.29** (91%). The structures of the disubstituted



Scheme 5.5

derivatives **5.30-5.32** and of the alkene **5.29** were confirmed by the ^{1}H and ^{13}C NMR spectra (Tables 5.9 and 5.10) and by their CHN microanalyses data. For compounds **5.30a,b** and **5.31**, the methylene protons α to the quaternary carbons displayed complex patterns again indicating that the hydrogens were nonequivalent. For the dibutyl derivative **5.30b**, the chemical shifts for the two protons were quite similar. However, for **5.30a**, the difference in the chemical shifts for the two protons was about 0.3 ppm.

Interestingly, for the phenylthio compound **5.32**, the signals appeared as a triplet, indicating the two protons were isochronous.

Hydrolysis of **5.30a,b** and **5.31** under the conditions described previously afforded the corresponding ketones **5.33a,b** and **5.34** (82-89%) (Table 5.5). As with the phenylthio derivative **5.15** where hydrolysis afforded the styryl derivative **5.12** (Scheme 5.3), the corresponding butyl analog **5.32** gave the alkene **5.35** (89%) which was obtained as a mixture of the E and Z isomers.

5.3 Experimental

Melting points were determined on a bristoline hot-stage microscope and are uncorrected. ^{1}H (300 MHz) NMR spectra were recorded on a Varian VXR-300 (FT mode) spectrometer with Me_4Si as internal standard. ^{13}C NMR spectra were recorded at 75 MHz on the same instrument using solvent peaks ($CDCl_3$, δ 77.0 or DMSO-d_6, δ 39.5) as references. IR spectra were run on a Perkin-Elmer 1600 FTIR spectrometer. High Resolution Mass Spectromery was carried out on a Finnigan Mat 95. Elemental analyses (C,H,N) were carried out using a Carlo Erba 1106 elemental analyzer. Flash chromatography was run on EM Science silica gel 60 (230-400 mesh).

The following compounds were prepared by literature procedures: 1-(benzotriazol-1-yl)-1-(carbazol-9-yl)-2-phenylethane **3.32a**, mp 129-130°C, lit. [89JHC829] mp 129-130°C; 1-(benzotriazol-1-yl)-1-(carbazol-9-yl)pentane **3.32d**, mp 135-137°C; lit. [91JOC2143] mp 135-137°C.

5.3.1 General Procedure for the Lithiation of **3.32a** and **3.32d** and Subsequent Reaction with Electrophiles

To a solution of **3.32a** or **3.32d** (10 mmol) in THF (80 mL) was added butyllithium (2.5 M in hexanes; 4.4 mL, 11 mmol) at -78 °C. The solution was stirred at -78 °C for 2 h and a solution of an appropriate electrophile (10 mmol) in THF (10 mL) was added (for **5.17** solution of $ClSiMe_3$ (1.4 mL, 11 mmol) in THF (10 mL) was also added). The reaction mixture was stirred at -78 °C for 4 h and at ambient temperature for 12 h. The reaction mixture was poured into saturated aqueous NH_4Cl (40 mL) and the aqueous layer extracted with Et_2O (3 x 30 mL). The combined organic fractions were washed with H_2O (1 x 30 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure to afford the crude product which was purified either by recrystallization or by column chromatography (see Tables 5.1 and 5.8).

N,3-Diphenyl-2-(carbazol-9-yl)prop-2-enethioamide **5.25** With phenyl isothiocyanate as the electrophile and **3.32a** as the precursor, **5.25** was obtained as yellow needles from hexanes (91%), mp 145-147 °C. ^1H NMR ($CDCl_3$): 8.76 (s, 1H), 8.48 (s, 1H), 8.16 (d, J = 5.9 Hz, 2H), 7.4-6.95 (m, 14H), and 6.77 (d, J = 7.6 Hz, 2H). ^{13}C NMR ($CDCl_3$): 191.6, 141.4, 138.6, 138.1, 132.8, 132.1, 130.1, 129.9, 128.7, 128.5, 127.1, 126.8, 124.3, 123.9, 121.2, 120.7, and 110.5. *Analysis* ($C_{27}H_{20}N_2S$): calcd: C, 80.17; H, 4.98; N, 6.92. Found: C, 80.00; H, 4.98; N, 6.80.

N-Phenyl-2-(carbazol-9-yl)hex-2-enethioamide **5.29** With phenyl isothiocyanate as the electrophile and **3.32d** as the precursor, **5.29** was obtained as yellow needles from hexanes (87%), mp 126-127 °C. ^1H NMR ($CDCl_3$): 8.47 (s, 1H), 8.2-8.0 (m, 3H), 7.5- 7.1 (m, 11H), 1.8-1.7 (m, 2H), 1.5-1.35 (m, 2H), and 0.75 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$): 190.7, 148.6, 140.0, 138.0, 134.8, 128.7, 127.1, 127.0, 126.7, 124.4, 123.5, 120.9, 120.8, 120.76, 120.7, 110.0, 31.2, 21.3, and 13.9. *Analysis* ($C_{24}H_{22}N_2S$): calcd: C, 77.80; H, 5.98; N 7.56. Found: C, 77.90; H, 6.06; N, 7.45.

5.3.2 General Procedure for Hydrolysis

To a solution of an appropriate intermediate (2.5 mmol) in THF (20 mL) and H_2O (10 mL) was added aqueous HCl (10 M; 1 mL). The mixture was stirred at ambient temperature for 24 h and extracted with Et_2O (3 x 20 mL). The organic layer was washed with H_2O (1 x 10 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure to give the crude product. The ketone was extracted from the residue with hexane (3 x 20 mL) and the solvent evaporated to give the crude product, which was purified by column chromatography (see Table 5.5).

1-(Carbazol-9-yl)-1-phenylthio-2-phenylethylene **5.12** Hydrolysis of **5.15** under the above conditions afforded **5.12** as colorless plates (column chromatography; hexanes as elutent) (92%), mp 120-122 °C. ^{1}H NMR ($CDCl_3$): 7.92 (d, J = 7.8 Hz, 2H), 7.44 (d, J = 8.1 Hz, 2H), 7.35- 7.25 (m, 2H), and 7.25-6.8 (m, 11H). ^{13}C NMR ($CDCl_3$): 139.1, 134.2, 133.7, 129.0, 128.4, 128.38, 128.34, 128.04, 128.0, 127.9, 125.8, 123.8, 120.3, 119.8, and 111.6. *Analysis* ($C_{26}H_{19}NS$): calcd: C, 82.72; H, 5.07; N, 3.71. Found: C, 82.65; H, 5.01; N, 3.45.

1-(Carbazol-9-yl)-1-phenylthiopent-1-ene **5.35** Hydrolysis of **5.32** under the above conditions afforded a mixture of the E and Z isomers **5.35** as a colorless oil (column chromatography; hexanes as elutent) (89%):

Major Isomer: ^{1}H NMR ($CDCl_3$): 7.94 (d, J = 7.7 Hz, 1.33H), 7.55-6.7 (m, 7.33H), 6.27 (t, J = 7.3 Hz, 0.67H), 2.64 (q, J = 7.3 Hz, 1.33H), 1.30 (hex, J = 7.4 Hz, 1.33H), and 0.72 (t, J = 7.3 Hz, 2H). ^{13}C NMR ($CDCl_3$): 140.0, 134.7, 133.6, 131.2, 128.4, 128.14, 125.6, 123.2, 119.9, 119.8, 110.8, 30.8, 22.0, and 13.6.

Minor Isomer: ^{1}H NMR ($CDCl_3$): 7.88 (d, J = 7.7 Hz, 0.67H), 7.55-6.7 (m, 3.67H), 6.13 (t, J = 7.5 Hz, 0.33H), 1.81 (q, J = 7.3 Hz, 0.67H), 1.65 (hex, J = 7.2 Hz, 0.67H), and 1.10 (t, J = 7.3 Hz, 1H). ^{13}C NMR ($CDCl_3$): 140.8, 135.2, 133.0, 130.3,

128.08, 127.7, 125.5, 122.9, 119.7, 119.6, 110.7, 31.3, 22.6, and 14.0. HRMS: $C_{23}H_{21}NS$ requires M^+ *m/z* 343.1394, found M^+ *m/z* 343.1387.

Table 5.1 Preparation of adducts **5.13**, **5.15**, **5.17**, **5.20a-c**, **5.21**, **5.23** and **5.26a-b**

Compd	Electrophile	mp (°C)	Yield (%)	Recryst. Solvent
5.13	4-MeC_6H_4CHO	156-158	87	EtOH
5.15	PhSSPh	170-172	95	MeOH
5.17	PhCHO/$CiSiMe_3$	130-131	67	a
5.20a	$PhCH_2Br$	145-147	86	a
5.20b	MeI	89-91	88	MeOH
5.20c	BuI	101-103	78	a
5.21	ClCOOEt	212-214	87	a
5.23	PhNCO	115-117	88	MeOH
5.26a	2-Cyclopentenone	105-107	76	a
5.26b	2-Cyclohexenone	187-189	81	a

[a] Column chromatography (silica gel; chloroform : hexane = 1 : 2).

Table 5.2 Microanalyses data of **5.13**, **5.15**, **5.17**, **5.20a-c**, **5.21**, **5.23** and **5.26a-b**

Compd	Molecular formula	C H N Required (%)	C H N Found (%)
5.13	$C_{34}H_{28}N_4O$	80.29 5.55 11.02	79.92 5.74 11.08
5.15	$C_{32}H_{24}N_4S$	77.36 4.87 11.28	77.54 4.88 11.32
5.17	$C_{36}H_{34}N_4OSi$	76.29 6.05 9.89	75.97 6.13 9.71
5.20a	$C_{33}H_{26}N_4$	82.84 5.44 11.71	82.53 5.51 11.45
5.20b	$C_{27}H_{22}N_4$	80.57 5.51 13.92	80.78 5.68 13.56
5.20c	$C_{30}H_{28}N_4$	81.39 6.53 12.48	81.05 6.35 12.60
5.21	$C_{29}H_{24}N_4O_2$	75.63 5.25 12.17	75.64 5.36 12.03
5.23	$C_{33}H_{25}N_5O$	78.09 4.96 13.80	77.71 4.98 13.62
5.26a	$C_{31}H_{26}N_4O$	79.12 5.57	79.20 5.98
5.26b	$C_{32}H_{28}N_4O$	79.31 5.82 11.56	78.90 5.80 11.39

Table 5.3 ^{1}H NMR data of adducts **5.13**, **5.15**, **5.17**, **5.20a-c**, **5.21**, **5.23** and **5.26a-b**

Compd	Aromatic CH signals	dd for CH^AH^B			Other signals
		δH^A	δH^B	J(Hz)	
5.13	8.15-7.90 (m, 3H), 7.26-6.83 (m, 12H), 6.81-6.57 (m, 5H), 6.18 (d, 2H, J=8.3Hz)	4.54	4.11	13.4	3.44 (d, 1H, J=4.6Hz), 2.21 (s, 2H)
5.15	8.11-7.91 (m, 3H), 7.30-6.50 (m, 9H)	4.69	4.54	14.0	
5.17	7.66 (d, 1H, J=8.4Hz), 7.09-6.35 (m, 21H)	4.19	3.93	13.7	5.76 (d, 1H, J=8.4Hz), -0.18 (s, 9H)
5.20a	8.15-7.92 (m, 3H), 7.28-6.85 (m, 14H), 6.76-6.42 (m, 5H)	4.58	4.33	13.5	
5.20b	8.12-8.01 (m, 3H), 7.24-6.92 (m, 11H), 6.60-6.51 (m, 3H)	4.85	4.33	13.0	2.53 (s, 3H)
5.20c	8.12-8.01 (m, 3H), 7.30-6.91 (m, 11H), 6.67-6.46 (m, 3H)	4.70	4.57	13.5	3.15-3.00 (m, 2H), 1.60-1.17 (m, 4H), 0.78 (t, 3H, J=7.3Hz)
5.21	8.10-7.97 (m, 3H), 7.25-6.68 (m, 12H), 6.07 (d, 2H, J=8.3Hz)	4.99	4.65	14.0	4.30-4.12 (m, 2H), 0.97-0.91 (m, 3H)
5.23	11.11 (s, 1H), 8.15-8.06 (m, 3H), 7.63-6.97 (m, 17H) 6.43 (d, 2H, J=7.1Hz)	4.87	4.64	12.0	
5.26a	8.09 (d, 2H, J=7.9Hz), 8.01 (d, 1H, J=8.4Hz), 7.2-7.0 (m, 8H), 6.91 (t, 3H, J=7.9Hz), 6.45 (d, 2H, J=7.1Hz), 6.20 (d, 1H, J=8.5Hz)	4.74	4.45	13.3	4.16 (m, 1H), 3.06 (d, 1H, J=17.4Hz), 2.67 (m, 1H), 2.47 (d, 1H, J=11.2), 2.3-1.8 (m, 3H)
5.26b	8.15-8.04 (m, 3H), 7.30-6.81 (m, 12H), 6.46-6.29 (m, 3H)	4.77	4.43	12.0	3.67-3.38 (m, 2H), 2.66-2.35 (m, 2H), 2.10-1.65 (m, 4H), 1.33-1.16 (m, 1H)

Table 5.4 ^{13}C NMR data of adducts **5.13**, **5.15**, **5.17**, **5.20a-c**, **5.21**, **5.23** and **5.26a-b**

	Benzotriazole						Carbazole									
Compd	C_4	C_5	C_6	C_7	C_{3a}	C_{7a}	C_1	C_2	C_3	C_4	C_{4a}	C_{9a}	>C<	Ph	CH_2	E
5.13	120.0	124.4	127.6	111.4	145.7	133.8	114.0	125.2	119.8	119.0	125.4	138.5	86.9	133.2 129.1 128.0 127.9	43.8	133.3 129.7 128.6 76.8 21.0
5.15	119.5	124.2	127.1	112.7	145.8	132.0	112.9	123.7	120.4	119.6	125.5	139.1	90.8	132.3 130.0 128.4 127.7	44.3	136.6 130.6 127.2 125.4
5.17	119.9	124.7	127.5	111.4	145.7	133.3	114.2	123.5	119.5	118.5	126.9	138.4	87.2	133.9 130.0 128.0 127.9	43.9	129.6 128.6 127.7 123.5 77.8 0.09
5.20a	120.1	124.3	127.5	110.6	146.5	132.9	112.5	124.1	120.3	120.1	126.1	139.8	83.5	133.2 130.3 128.1 127.8	41.5	
5.20b	120.0	124.2	127.3	110.7	146.8	132.1	112.3	124.3	120.3	120.1	126.2	139.9	82.2	134.0 130.4 128.0 127.7	43.7	27.9
5.20c	120.1	124.2	127.4	110.7	146.7	132.3	112.6	124.3	120.2	120.1	126.2	139.9	85.3	134.0 130.1 128.1 127.6	40.6	37.0 25.7 22.3 13.8
5.21	119.6	124.4	127.1	111.4	146.5	132.8	114.3	123.7	120.2	119.8	125.6	139.5	82.5	133.2 131.3 127.5 127.4	40.2	165.6 63.3 13.5
5.23	121.1	124.9	128.1	111.4	145.4	131.7	112.0	125.2	120.6	120.5	126.7	140.6	86.4	132.8 130.0 128.3 128.1	45.6	164.3 136.4 129.2 128.9 128.2 125.2 121.1
5.26a[a]	120.6	124.2	127.2	112.1	146.3	134.0	113.1	126.2	120.1	120.0	b	b	86.6	133.5 129.9 128.2 (2)	45.1	214.1 42.8 42.0 37.8 26.4
5.26b	120.7	124.2	127.4	112.4	146.2	134.4	113.0	124.2	120.1	119.9	126.1	139.8	87.5	133.4 130.3 128.1 127.4	44.9	208.8 40.7 40.1 28.9 23.8

[a] Spectrum run at 45°C. [b] Signals not observed due to low intensity.

Table 5.5 Preparation of ketones **5.14a,b**, **5.22a-c**, **5.24** , **5.27a,b**, **5.33a,b** and **5.34**

Compd	R	mp (°C) or bp (°C/mmHg)	Lit. mp (°C) or bp (°C/mmHg)	Yield (%)	Molecular formula	C H N Required (%)	C H N Found (%)
5.14a	Ph	77-79	----	57	$C_{15}H_{14}O_2$	79.62 6.24	79.56 6.23
5.14b	4-Me-C_6H_4	90-91	----	51	$C_{16}H_{16}O_2$	79.97 6.71	80.21 6.72
5.22a	$PhCH_2$	oil	118-120/0.1[a]	63	$C_{15}H_{14}O$	---- ----	---- ----
5.22b	Me	107-109/24	109-112/24[b]	77	$C_9H_{10}O$	---- ----	---- ----
5.22c	Bu	112-114/5	110-112/5[c]	82	$C_{12}H_{16}O$	---- ----	---- ----
5.24	-	127-129	----	62	$C_{15}H_{13}NO_2$	75.30 5.48 5.89	75.42 5.31 6.26
5.27a	(n=1)	oil	----	51	$C_{13}H_{14}O_2$	HRMS: 202.0994	202.0985
5.27b	(n=2)	oil	----	67	$C_{14}H_{16}O2$	HRMS: 216.1150	216.1150
5.33a	Me	126-127/760	127/760[d]	86	$C_6H_{12}O$	---- ----	---- ----
5.33b	Bu	49-51/0.5	88/22[e]	89	$C_9H_{18}O$	---- ----	---- ----
5.34	-	99-101	----	82	$C_{12}H_{15}NO_2$	70.23 7.37 6.82	70.63 7.46 6.78

[a] Olah, G. A.; Mehrotra, A. K.; Narang, S. C. *Synthesis,* **1982**, 151. [b] Julian, P. L.; Oliver, J. J. *Organic Synthesis,* **1938**, *18*, 54. [c] Niinobe, S. *J. Pharm. Soc. Japan,* **1943**, *63*, 204. [d] *Dic. of Org. Compds,* fifth edition, Chapman and Hall, **1982**, p2932. [e] Briese, R. R. *J. Am. Chem. Soc.* **1933**, *55*, 1697.

Table 5.6 ^{1}H NMR data of Ketones **5.14a,b**, **5.22a-c**, **5.24**, **5.27a,b**, **5.33a,b** and **5.34**

5.14a	7.46-7.20 (m, 8H), 7.06-6.95 (m, 2H), 5.18 (d, 1H, J=4.4Hz), 4.25 (d, 1H, J=4.4Hz), 3.63 (s, 2H)
5.14b	7.30-7.24 (m, 3H0, 7.20 (s, 4H), 7.05-6.98 (m, 2H), 5.15 (d, 1H, 4.2Hz), 4.21 (d, 1H, J=4.2Hz), 3.63 (s, 2H), 2.37 (s, 3H)
5.22a	7.31-7.20 (m, 6H), 7.15-7.05 (m, 4H), 3.66 (s, 4H)
5.22b	7.40-7.13 (m, 5H), 3.69 (s, 2H), 2.15 (s, 3H)
5.22c	7.35-7.14 (m, 5H), 3.66 (s, 2H), 2.43 (t, 2H, J=7.4Hz), 1.53 (quintet, 2H,, J=7.4Hz), 1.24 (sextet, 2H, J=7.5Hz), 0.85 (t, 3H, J=7.3Hz)
5.24	8.74 (bs, 1H), 7.67-7.61 (m, 2H), 7.43-7.14 (m, 8H), 4.31 (s, 2H)
5.27a	7.36-7.19 (m, 5H), 3.79 (s, 2H), 3.33 (q, 1H, J=8.3Hz), 2.50-1.95 (m, 6H)
5.27b	7.32-7.09 (m, 5H), 3.68 (s, 2H), 2.98-2.86 (m, 1H), 2.50-2.38 (m, 1H), 2.32-2.14 (m, 3H), 2.05-1.87 (m, 2H), 1.70-1.52 (m, 2H)
5.33a	2.43 (t, 2H, J=7.2Hz), 2.13 (s, 3H), 1.60-1.51 (m, 2H), 1.36-1.28 (m, 2H), 0.91 (t, 3H, J=7.3Hz)
5.33b	2.40 (t, 4H, J=7.3Hz), 1.55 (quintet, 4H, J=7.2Hz), 1.30 (sextet, 4H, J=7.3Hz), 0.91 (t, 6H, J=7.2Hz)
5.34	8.86 (bs, 1H), 7.64 (d, 2H, J=7.3Hz), 7.41-7.30 (m, 2H), 7.19-7.10 (m, 1H), 2.99 (t, 2H, J=7.3Hz), 1.62 (quintet, 2H, J=7.6Hz), 1.36 (sextet, 2H, J=7.5Hz), 0.92 (t, 3H, J=7.3Hz)

Table 5.7 ^{13}C NMR of Ketones **5.14a,b**, **5.22a-c**, **5.24**, **5.27a,b**, **5.33a,b** and **5.34**

5.14a	206.9 137.5 132.8 129.3 129.1 128.9 128.6 127.7 127.2 79.2 44.6
5.14b	207.1 138.7 134.6 132.9 129.7 129.3 128.6 127.6 127.2 78.9 44.5 21.2
5.22a	205.3 133.8 129.3 128.4 126.8 48.9
5.22b	206.4 134.2 129.3 128.7 127.0 51.0 29.2
5.22c	208.6 134.3 129.3 128.6 126.8 50.0 41.6 25.7 22.1 13.7
5.24	196.2 157.3 136.2 132.4 129.8 129.2 128.7 127.3 125.3 119.7 42.7
5.27a	216.3 208.0 133.4 129.3 128.7 127.1 48.9 46.7 40.2 37.3 25.9
5.27b	209.8 207.9 133.4 129.3 128.8 127.2 49.2 48.3 42.6 40.8 27.3 24.8
5.33a	208.9 43.2 29.5 25.7 22.1 13.6
5.33b	211.4 42.4 25.9 22.3 13.7
5.34	199.4 157.6 136.3 129.0 125.1 119.7 36.0 25.3 22.1 13.7

Table 5.8 Preparation of adducts **5.30a,b**, **5.31** and **5.32**

Compd	Electrophile	mp (°C)	Yield (%)	Molecular formula	C	H	N	C	H	N
					Required (%)			Found (%)		
5.30a	MeI	138-140	91[a]	$C_{24}H_{24}N_4$	78.23	6.59	15.10	77.97	6.59	15.10
5.30b	BuI	158-160	94[a]	$C_{27}H_{30}N_4$	78.99	7.39	13.65	78.85	7.55	13.70
5.31	PhNCO	122-124	86[b]	$C_{30}H_{27}N_5O$	76.09	5.75	14.79	75.96	5.95	14.51
5.32	PhSSPh	159-161	94[a]	$C_{29}H_{26}N_4S$	75.29	5.66	12.11	75.41	5.65	11.90

[a] Recrystallized from methanol. [b] Purified by column chromatography (silica gel; $CHCl_3$: hexane = 1 : 2).

Table 5.9 ^{1}H NMR data of adducts **5.30a,b**, **5.31** and **5.32**

5.30a	8.11-8.00 (m, 3H), 7.27 (m, 7H), 7.00-6.94 (m, 1H), 6.60 (d, 1H, J=8.5Hz), 3.57-3.45 (m, 1H), 3.25-3.10 (m, 1H), 2.66 (s, 3H), 1.36-0.85 (m, 4H), 0.75 (t, 3H, J=6.9Hz)
5.30b	8.10-7.97 (m, 3H), 7.29-7.13 (m, 7H), 6.99-6.91 (m, 1H), 6.61 (d, 1H, J=8.5Hz), 3.50-3.17 (m, 4H), 1.45-0.80 (m, 11H), 0.75 (t, 3H, J=7.3Hz)
5.31	11.04 (s, 1H), 8.13-8.05 (m, 3H), 7.67-7.58 (m, 2H), 7.47-7.12 (m, 11H), 6.81 (d, 1H, J=7.6Hz), 3.60-3.25 (m, 2H), 1.55-0.76 (m, 7H)
5.32	8.01 (d, 3H, J=7.3Hz), 7.30-6.80 (m, 13Hz), 6.57 (d, 1H, J=8.6Hz), 3.20 (t, 2H, J=8.0Hz), 1.95-1.76 (m, 1H), 1.44-1.21 (m, 2H), 0.84 (t, 3H, J=7.3Hz)

Table 5.10 ^{13}C NMR data of adducts **5.30a,b**, **5.31** and **5.32**

	Benzotriazole						Carbazole							
Compd	C_4	C_5	C_6	C_7	C_{3a}	C_{7a}	C_1	C_2	C_3	C_4	C_{4a}	C_{9a}	>C<	Other signals
5.30a	119.9	124.6	127.5	110.7	146.8	132.0	112.4	124.1	120.3	120.1	126.2	139.7	82.5	39.4 27.6 25.5 22.4 13.7
5.30b	119.9	124.6	127.4	110.7	146.7	132.1	112.6	124.1	120.2	120.1	126.5	140.4	85.7	35.9 25.5 22.5 13.7
5.31	120.2	124.8	127.8	109.6	145.7	132.7	112.0	124.1	120.8	120.4	126.5	140.4	86.0	164.7 136.7 129.1 125.3 39.3 26.4 22.3 13.7
5.32	119.8	124.5	127.8	111.0	146.7	132.3	113.6	124.4	120.8	120.1	126.0	139.8	91.9	137.2 130.2 128.6 126.0 39.5 26.2 22.2 13.9

CHAPTER VI
3-DIALKYLAMINO-1-(BENZOTRIAZOL-1-YL)-1-(CARBAZOL-9-YL)PROPANES: NOVEL β-AMINOACYL SYNTHON EQUIVALENTS

6.1 Introduction

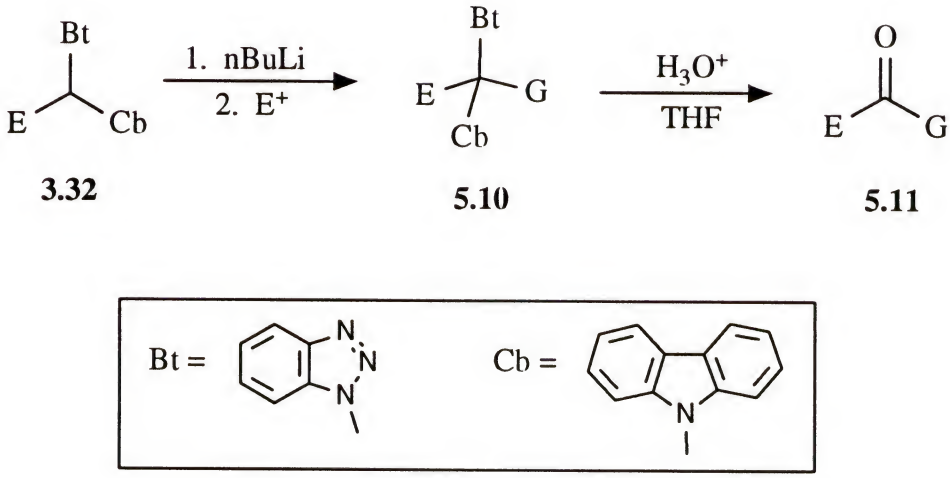
β-Aminoethyl ketones have been widely used as precursors for *in situ* generation of the relatively unstable and reactive vinyl ketones required for Robinson annulation type reactions of *e.g.* cyclohexanones [57JOC291] or 1,3-diketones [74S51] for constructing carbocyclic rings in organic synthesis [77JSOC(Jpn)1009].

Few α'-(functionalized alkyl) β-aminoethyl ketones have been reported in the literature. Most of the β-aminoethyl ketones [73S703] have been prepared by the treatment of simple ketones such as acetone, acetophenone with amines in the presence of formaldehyde, and lack other functionality. α'-Hydroxy β-aminoethylketones have been prepared by aminomethylation of tertiary acetylcarbinols [59JGC(USSR)765]; there has been no report of the synthesis of any of the title ketones *via* acyl anion equivalents.

6.2 Results and Discussion

In Chapter V, we have demonstrated the use of substituted (benzotriazol-1-yl)(carbazol-9-yl)methanes **3.32** as acyl anion equivalents (Scheme 6.1). The benzyl and the butyl derivatives readily underwent deprotonation with butyllithium and the anion reacted readily with alkyl halides, aldehydes and isocyanates to afford the expected intermediates. These were then hydrolyzed under mild acidic conditions to form the corresponding ketones **5.11**. If a β-aminoethyl

group is attached to **3.32**, then this system should act as a synthetic equivalent for the synthesis of β-amino ketones.

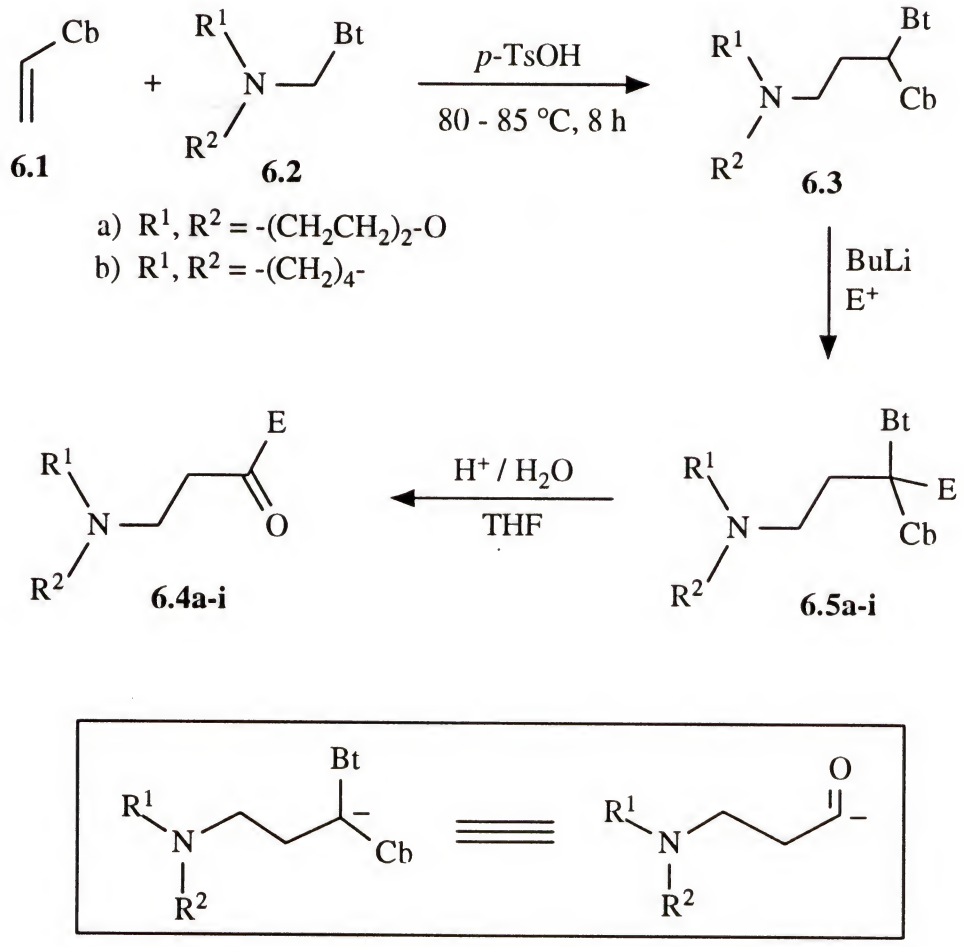


3.32 **5.10** **5.11**

Scheme 6.1

Other studies in our laboratory have demonstrated that α-(benzotriazol-1-yl)alkylamines of type **6.2** undergo polar additions to enol ethers [92JOC4932] and also to enamines including N-vinylcarbazole [92UP1] to afford adducts **6.3** (Scheme 6.2). Employing conditions similar to those described previously [91JOC6917], the morpholino derivative **6.3a** underwent smooth deprotonation with butyllithium at -78 °C to give the corresponding carbanion which reacted readily with alkyl and benzyl halides to afford the corresponding products **6.5a-d** in yields of 74-86% (Scheme 6.2 and Table 6.1). As in our previous work [91JOC2143; 91JOC6917], to obtain reasonable yields with aldehydes, we trapped the reaction intermediate with trimethylsilyl chloride (TMSCl) to give the corresponding stable silyl ether derivatives **6.5e-g** (57-68%) (see Table 6.1). Similarly, the anion of the pyrrolidino derivative **6.3b** reacted with benzyl bromide and with octyl iodide to afford

6.5h (69%) and **6.5i** (71%). The crude products **6.5a-i** were subjected to a preliminary purification on silica gel to remove unwanted impurities.



Scheme 6.2

Hydrolysis of the intermedite products **6.5a-i** was readily achieved at ambient temperature in the presence of dilute hydrochloric acid. Careful control of pH during workup enabled easy removal of carbazole and benzotriazole and afforded essentially pure β-aminoethyl ketones **6.4a-i** in high yields (82-96%) (see Table 6.2). The ketones **6.4a-i** were characterized by their NMR and HRMS data (see Tables 6.3 and 6.4). The

^{1}H and ^{13}C NMR spectra displayed the expected patterns for the respective compounds. In general, the carbonyl signals were observed between 207.0 and 211.7 ppm in the ^{13}C NMR spectra. Absence of the heterocyclic signals indicated that the β-aminoethyl ketones obtained were essentially pure after workup.

The use of substituted (benzotriazol-1-yl)(carbazol-9-yl)methanes as acyl anion equivalents has been extended to the synthesis of β-aminoethyl ketones. The high yields and purity of the final products together with the lack of necessity for purification of the intermediates makes this route an attractive system for further exploration.

6.3 Experimental

Melting points were determined on a Bristoline hot-stage microscope and are uncorrected. ^{1}H (300 MHz) NMR spectra were recorded on a Varian VXR-300 (FT mode) spectrometer with Me_4Si as internal standard. ^{13}C NMR spectra were recorded at 75 MHz on the same instrument using solvent peaks ($CDCl_3$, δ 77.0 or DMSO-d_6, δ 39.5) as references. High Resolution Mass Spectrometry was carried out on a Finnigan Mat 95. Elemental analyses (C,H,N) were carried out using a Carlo Erba 1106 elemental analyzer. Flash chromatography was run on EM Science silica gel 60 (230-400 mesh).

The following compounds were prepared by known literature procedures: 1-[(benzotriazol-1-yl)methyl]morpholine **6.2a**, mp 104-105°C, lit. [89OPPI135] mp 103-104°C; 1-[(benzotriazol-1-yl)methyl]pyrrolidine **6.2b**, mp 80-81°C, lit. [89OPPI135] mp 79-81°C.

6.3.1 General Procedure for the Preparation of 3-Dialkylamino-1-(benzotriazol-1-yl)-1-(carbazol-9-yl)propanes

A mixture of an appropriate amine **6.2a** or **6.2b** (25 mmol), N-vinylcarbazole **6.1** (25 mmol) and *p*-TsOH (0.1 g) was heated to 80 °C. The mixture was stirred at 80-85 °C for 8 h, cooled to room temperature and the crude product purified by chromatography ($CHCl_3$) or by recrystallization to afford the pure products. The following compounds were prepared in this manner:

1-(Benzotriazol-1-yl)-1-(carbazol-9-yl)-3-morpholinopropane **6.3a**, colorless needles from EtOH (43%), mp 145-147°C. ^1H NMR ($CDCl_3$): 8.1- 7.95 (m, 3H), 7.7-7.55 (m, 3H), 7.45-7.35 (m, 2 H), 7.3-7.1 (m, 5 H), 3.7- 3.6 (m, 4 H), 3.45-3.35 (m, 2 H), 2.5-2.4 (m, 3 H), and 2.15-2.05 (m, 3 H). ^{13}C NMR ($CDCl_3$): 146.3, 139.0, 133.1, 127.9, 126.2, 124.3, 123.7, 120.5, 120.3, 120.0, 110.1, 109.7, 67.0, 65.9, 53.5, 53.4, and 27.7. Anal. Cal'd for $C_{25}H_{27}N_5O$: C, 72.61; H 6.58; N, 16.94. Found: C, 72.96; H, 6.27; N, 16.96.

1-(Benzotriazol-1-yl)-1-(carbazol-9-yl)-3-pyrrolidinopropane **6.3b**, colorless plates from Et_2O/hexane (26%), mp 127- 129 °C: ^1H NMR ($CDCl_3$): 8.08- 7.94 (m, 3 H), 7.75-7.56 (m, 3 H), 7.48-7.34 (m, 2 H), 7.28-7.01 (m, 5 H), 3.50-3.30 (m, 2 H), 2.52-2.20 (m, 6 H), and 1.74 (s, br, 4 H). ^{13}C NMR ($CDCl_3$): 146.6, 139.9, 133.4, 128.0, 126.5, 124.5, 123.9, 120.7, 120.5, 120.2, 110.4, 110.1, 66.3, 54.1, 51.1, 30.6, and 24.1. Anal. Cal'd for $C_{25}H_{25}N_5$: C, 75.92; H 6.37; N, 17.71. Found: C, 75.53; H, 6.40; N, 17.67.

6.3.2 General Procedure for the Lithiation of **6.3** and Subsequent Reaction with Electrophiles

To a solution of **6.3a** or **6.3b** (10 mmol) in THF (80 mL) was added butyllithium (2.5 M in hexanes; 4.4 mL, 11 mmol) at -78 °C. The solution was stirred at -78 °C for 2 h and a solution of an appropriate electrophile (10 mmol) in THF (10 mL) was added (for **6.5e-g** a solution of TMSCl (1.4 mL, 11 mmol) in THF (10 mL) was also added). The reaction was stirred at -78 °C for 4 h and at ambient temperature for 12 h. The reaction mixture was poured into saturated aqueous NH_4Cl (40 mL) and the aqueous layer extracted with Et_2O (3 x 30 mL). The combined organic fractions were washed with H_2O (1 x 30 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure to afford the crude product which was subjected to a preliminary purification by column chromatography ($CHCl_3$) (see Table 6.1).

6.3.3 General Procedure for the Hydrolysis of Adducts **6.5**

To a solution of an appropriate intermediate **6.5** (5 mmol) in THF-H_2O (20 + 10 mL) was added aqueous HCl (5 M; 2 mL). The solution was stirred at room temperature for 3 h (TLC showed the complete disappearence of the starting material), and then aqueous HCl (1 M; 10 mL) was added. The whole reaction mixture was washed with Et_2O (3 x 10 mL), the aqueous phase neutralized with Na_2CO_3 until pH = 9 and extracted with CH_2Cl_2 (3 x 20 mL). The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure to give the pure products **6.4a-i** as colorless oils which were characterized by their ^1H and ^{13}C NMR spectra and by their high resolution mass spectral data (see Tables 6.2-6.4).

Table 6.1 Preparation of adducts **6.5a-i**

Compd	R^1, R^2	Electrophile	Yield (%)	mp (°C)
6.5a	$-(CH_2)_2O(CH_2)_2-$	$PhCH_2Br$	78	101-104
6.5b	$-(CH_2)_2O(CH_2)_2-$	$4\text{-}MeC_6H_4CH_2Br$	74	119-121
6.5c	$-(CH_2)_2O(CH_2)_2-$	$n\text{-}CH_3(CH_2)_5I$	86	104-106
6.6d	$-(CH_2)_2O(CH_2)_2-$	$n\text{-}CH_3(CH_2)_7I$	82	96-99
6.5e	$-(CH_2)_2O(CH_2)_2-$	PhCHO/TMSCl	61	92-96
6.5f	$-(CH_2)_2O(CH_2)_2-$	$4\text{-}MeC_6H_4CHO$/TMSCl	68	101-106
6.5g	$-(CH_2)_2O(CH_2)_2-$	$c\text{-}C_6H_{11}CHO$/TMSCl	57	106-108
6.5h	$-(CH_2)_4-$	$PhCH_2Br$	69	96-98
6.5i	$-(CH_2)_4-$	$n\text{-}CH_3(CH_2)_7I$	71	86-89

Table 6.2 Preparation of ketones **6.4a-i**

Compd	Yield (%)	Molecular formula	HRMS required	HRMS found
6.4a	92	$C_{14}H_{19}NO_2$	233.1416	233.1416
6.4b	87	$C_{15}H_{21}NO_2$	247.1572	247.1574
6.4c	96	$C_{13}H_{25}NO_2$	228.1963	228.1959
6.4d	94	$C_{15}H_{29}NO_2$	255.2198	255.2202
6.4e	89	$C_{14}H_{19}NO_3$	249.1365	249.1364
6.4f	88	$C_{15}H_{21}NO_3$	263.1521	263.1519
6.4g	82	$C_{14}H_{25}NO_3$	255.1834	255.1829
6.4h	84	$C_{19}H_{19}NO$	217.1467	217.1475
6.4i	91	$C_{15}H_{29}NO$	239.2250	239.2258

Table 6.3 ^{1}H NMR data of ketones **6.4a-i**

6.4a	7.35-7.19 (m, 5H), 3.71 (s, 2H), 3.64 (t, 4H, J=4.6Hz), 2.62 (s, 4H), 2.41-2.34 (m, 4H)
6.4b	7.18-7.06 (m, 4H), 3.07-3.60 (m, 6H), 2.61 (s, 4H), 2.41-2.35 (m, 4H), 2.32 (s, 3H)
6.4c	3.75-3.67 (m, 4H), 2.70-2.55 (m, 4H), 2.48-2.40 (m, 6H), 1.64-1.53 (m, 2H), 1.36-1.22 (m, 6H), 0.92-0.85 (m, 3H)
6.4d	3.75-3.60 (m, 4H), 2.70-2.55 (m, 4H), 2.48-2.35 (m, 6H), 1.65-1.50 (m, 2H), 1.27 (s, 10H), 0.91-0.80 (m, 3H)
6.4e	7.42-7.25 (m, 5H), 5.10 (s, 1H), 4.55 (s, br, 1H), 3.65-3.59 (m, 4H), 2.60-2.46 (m, 4H), 2.38-2.29 (m, 4H)
6.4f	7.25-7.16 (m, 4H), 5.07 (s, 1H), 4.50 (s, br, 1H), 3.67-3.58 (m, 4H), 2.61-2.50 (m, 4H), 2.40-2.30 (m, 7H)
6.4g	3.99 (d, 1H, J=3.1Hz), 3.69 (t, 4H, J=4.6Hz), 2.77-2.60 (m, 4H), 2.55-2.42 (m, 4H), 1.85-1.60 (m, 5H), 1.50-1.10 (m, 6H)
6.4h	7.47-7.19 (m, 5H0, 3.70 (s, 2H), 2.75-2.61 (m, 4H), 2.49-2.40 (m, 4H), 1.80-1.68 (m, 4H)
6.4i	2.76-2.70 (m, 2H), 2.68-2.60 (m, 2H), 2.54-2.40 (m, 6H), 1.81-1.75 (m, 6H), 1.64-1.52 (m, 2H), 1.27 (s, 10H), 0.91-0.85 (m, 3H)

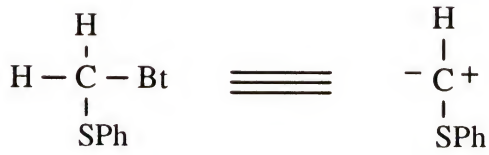
Table 6.4 ^{13}C NMR data of ketones **6.4a-i**

Compd	C=O	NR^1R^2	$NC_\alpha C_\beta$	E
6.4a	207.0	66.8 53.4	53.0 39.1	134.0 129.3 128.7 127.0 50.3
6.4b	207.3	66.8 53.4	53.0 38.9	136.5 130.9 129.3 129.1 49.9 20.9
6.4c	209.9	66.8 53.5	53.1 39.9	43.0 31.5 28.8 23.6 22.4 13.9
6.4d	209.9	66.8 53.5	53.1 39.9	43.0 31.7 29.3 29.1 29.0 23.6 22.5 14.0
6.4e	208.5	66.6 53.3	53.1 35.2	137.8 128.9 128.6 127.2 79.8
6.4f	208.7	66.6 53.3	53.1 35.2	138.4 134.8 129.5 127.1 79.6 21.0
6.4g	211.7	66.7 53.4	53.4 35.9	80.9 41.2 29.8 26.4 25.9 25.8 25.5
6.4h	207.2	54.0 23.3	50.4 41.4	134.1 129.3 128.6 126.9 50.2
6.4i	209.9	53.9 23.6	50.4 42.1	42.8 31.6 29.2 29.0 28.9 23.3 13.9

CHAPTER VII
(BENZOTRIAZOL-1-YL)PHENYLTHIOMETHANE: A 1,1-DIPOLE SYNTHON EQUIVALENT IN AROMATIC ANNULATIONS

7.1 Introduction

Development of new synthetic approaches which result in the annulation of carbocyclic derivatives incorporating latent functionality has gained increased attention due to their potential application in the synthesis of complex organic compounds [80JA7929, 81JA6529, 86JA1334, 86TL3483]. Recently, aromatic annulations mediated by 1,3-benzodithiolium and naphtho[1,8-de]-1,3-dithiin carbocations have been reported [90JOC5078, 90T2111]. In both cases, a carbonyl group was liberated after acidic hydrolysis of the resulting cyclization products. Work in our laboratory has demonstrated that the benzotriazolyl group in the compounds of type BtCH(R)X (where X = NR^1R^2, $NHCOR^3$, or SPh) can be removed under Lewis acid catalyzed conditions to afford the corresponding carbocations [91JOC4439, 92Sip, 92T4971]. Trapping these cations with electron-rich aromatics or C-H acids *in situ* produces the corresponding amino-, amido- or thio-alkylated products in good yields.



7.1

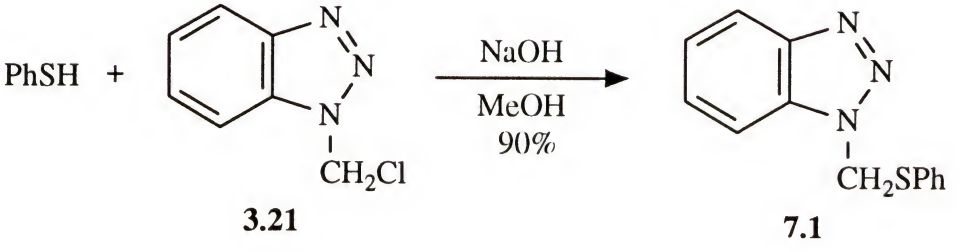
Bt = Benzotriazol-1-yl

Scheme 7.1

(Benzotriazol-1-yl)phenylthiomethane **7.1** has been shown to undergo deprotonation with *n*-butyllithium to afford a carbanion which reacts with a variety of electrophiles [87JCS(P1)781]. The ease with which the carbanion can be generated together with the facile removal of benzotriazolyl group to form a carbocation initiated an investigation into the participation of this species as a 1,1-dipole synthon equivalent in aromatic annulations (Scheme 7.1).

7.2 Results and Discussion

(Benzotriazol-1-yl)phenylthiomethane **7.1** was prepared by the reaction of 1-chloromethylbenzotriazole with phenylthiolate in MeOH [87JCS(P1)781]. The compound was easily recrystallized from methanol to give white crystals, mp 79-80°C (Scheme 7.2).

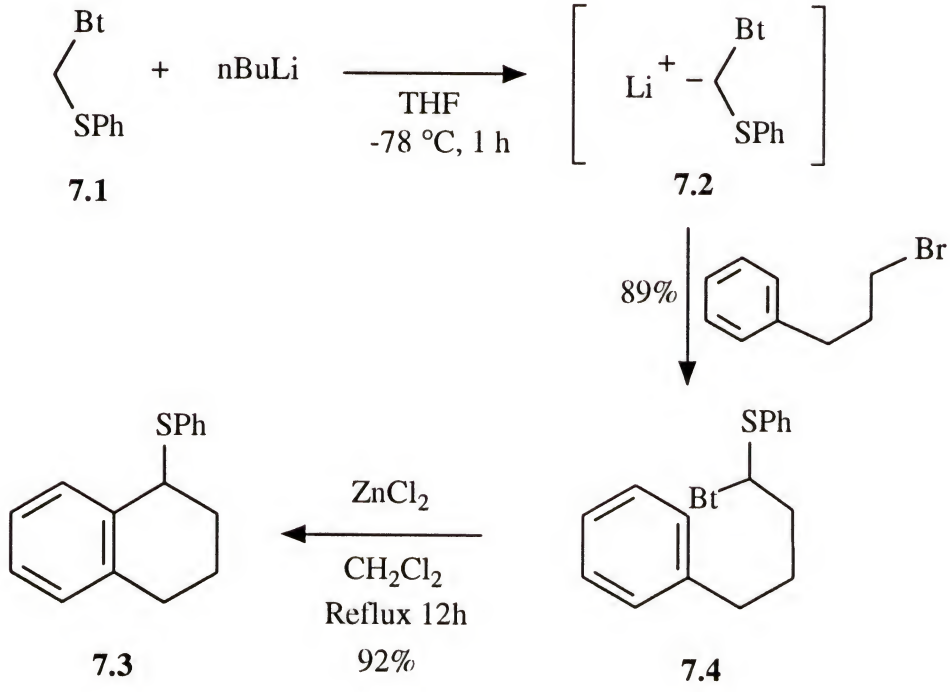


3.21 **7.1**

Scheme 7.2

Treatment of (benzotriazol-1-yl)phenylthiomethane **7.1** with *n*-butyllithium in THF at -78°C for 1h produced carbanion **7.2** which was then reacted with 1-bromo-3-phenylpropane to yield the intermediate product **7.4** in 89% yield (Scheme 7.3). Initial experiments employing aluminum chloride as the Lewis acid gave an unexpected result. Even under mild conditions (methylene chloride at room temperature for 10 mins), the starting material was completely consumed and complex

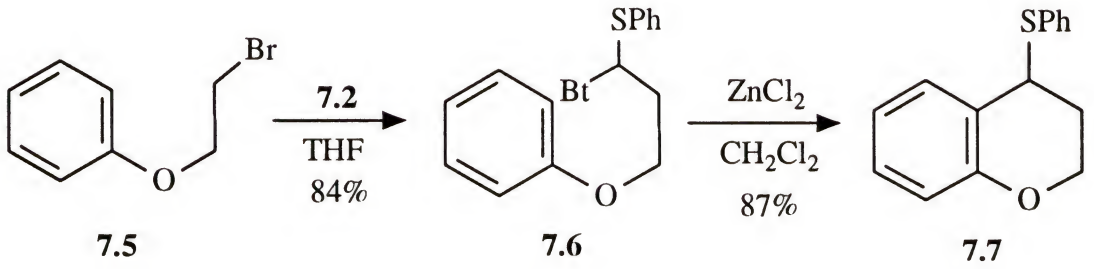
mixtures resulted. To attenuate the Lewis acidity, zinc chloride was used as the catalyst. The reaction went to completion in 12 h in refluxing methylene chloride and gave the expected cyclization product **7.3** in a yield of 92%. The liberated benzotriazole was easily removed from the reaction mixture by simple extraction with dilute aqueous sodium hydroxide. The structure of **7.3** was confirmed by ^{1}H and ^{13}C NMR and its high resolution mass spectral data.



Scheme 7.3

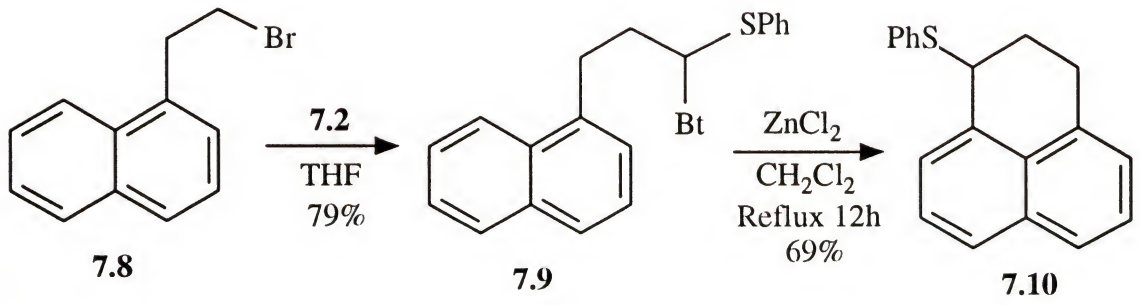
Considering the prevelence of oxygen heteroatoms in the carbon skeletons of some natural products, we were interested in the effect of an oxygen atom in the intervening chain. Thus, alkylation of anion **7.2** with β-bromophenetole **7.5** under similar conditions used above produced the requisite intermediate **7.6** in 84% yield.

Treatment of **7.6** with two equivalents of zinc chloride smoothly resulted in the desired cyclization product **7.7** in a yield of 87% (Scheme 7.4).



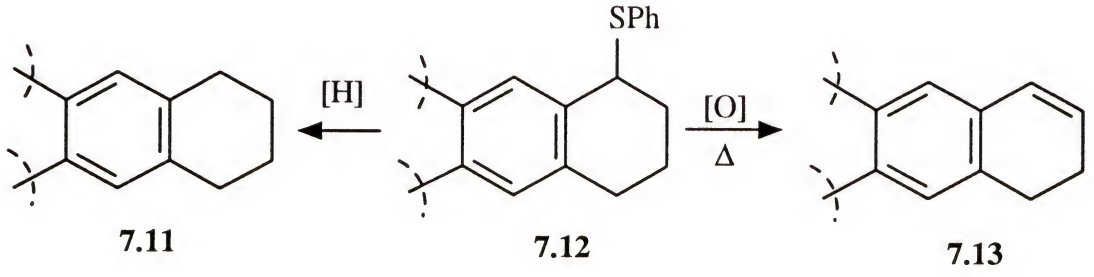
Scheme 7.4

Variation of the aromatic ring was briefly examined. As shown in scheme 7.5, reaction of anion **7.2** with 2-(1-naphthyl)ethyl bromide **7.8** produced the alkylated product **7.9** in 79%. Subsequent cyclization could give rise to either the five or six-membered ring product. Treatment of **7.9** with zinc chloride in methylene chloride resulted only in the formation of the six-membered ring compound **7.10**, presumably because geometric constraints disfavored a 5-*endo-trig* cyclization.



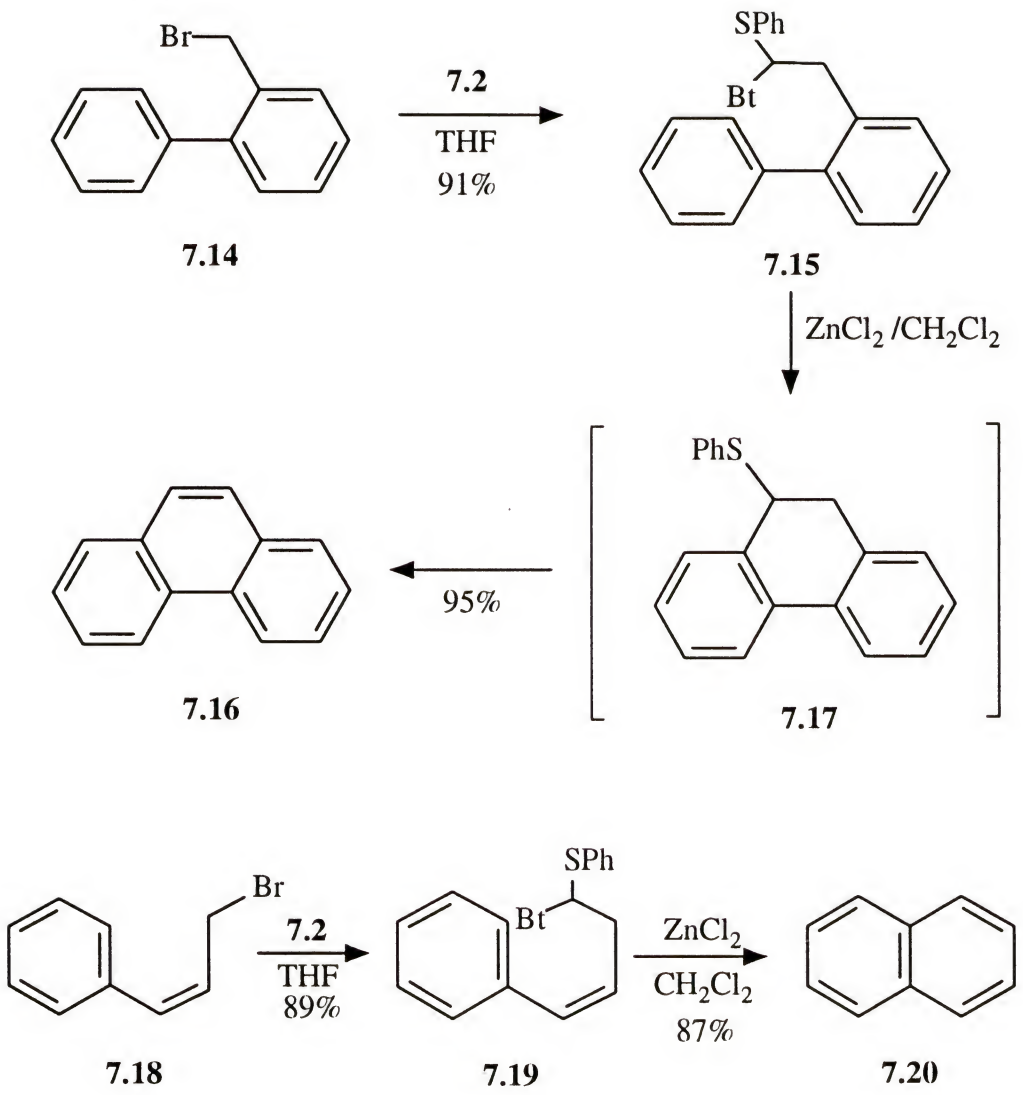
Scheme 7.5

The resistance of the phenylthio group to Lewis acid catalysed elimination and its subsequent presence in the cyclization product described herein provides further opportunities for synthetic elaborations (Scheme 7.6).



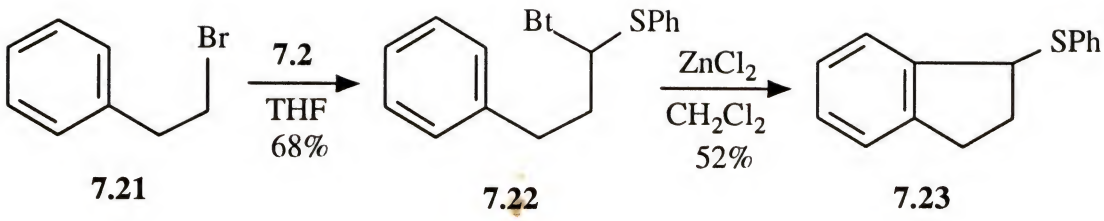
Scheme 7.6

To assess the phenylthio group's stability in a pro-aromatic environment, the cyclization of compound **7.15**, obtained from reaction of anion **7.2** with 2-bromomethylbiphenyl **7.14**, was carried out with zinc chloride in methylene chloride (Scheme 7.7). After refluxing for 12h, phenanthrene was the only isolated product. Shorter reaction time did not afford the expected cyclization product **7.17**, instead, a mixture of **7.15** and phenanthrene **7.16** was observed. The ensuing aromaticity was presumably the driving force for this behavior. A similar result was observed in the cyclization of compound **7.19** obtained from the reaction of anion **7.2** with cinnamyl bromide **7.18**.



Scheme 7.7

Extension of this method to include a five-membered ring annulation has been successful. Alkylation of anion **7.2** with 2-phenylethyl bromide **7.21** produced the intermediate **7.22** in 68% yield. While slower than the cyclization of **7.4**, **7.22** was indeed converted to the expected product **7.23** in a yield of 52% after a longer period of reflux (Scheme 7.8).



Scheme 7.8

The ability of (benzotriazol-1-yl)phenylthiomethane as a 1,1-dipole synthon equivalent to furnish aromatic annulations extends the application of benzotriazole derivatives in organic synthesis. The merit of this method relies on the simple synthetic availability and suitable reactivity of the title compound, as well as the mild reaction conditions employed in these cyclization procedures (even without the presence of activating groups on the aromatic ring). It is expected that this method will find useful applications in the construction of some complex molecules.

7.3 Experimental

Melting points were determined on a Bristoline hot-stage microscope and are uncorrected. ^{1}H NMR spectra were recorded on a Varian VXR-300 spectrometer ($CDCl_3$ as solvent) with TMS as internal reference. ^{13}C NMR spectra were recorded at 75 MHz on the same instrument using solvent peak ($CDCl_3$, δ = 77.0 ppm) as reference. Microanalyses were carried out using a Carlo Erba 1106 elemental analyser. High Resolution Mass Spectrometry was carried out on a Finnegan Mat 95.

The following compound was prepared by a known literature procedure: (benzotriazol-1-yl)phenylthiomethane **7.1**, mp 79-80°C, (Lit. [87JCS(P1)781] mp 80°C).

7.3.1 Lithiation of (Benzotriazol-1-yl)phenylthiomethane and Reaction with Alkyl Halides. General Procedure

Butyllithium (4.4 ml, 2.5 M in hexane, 11 mmol) was added to a solution of (benzotriazol-1-yl)phenylthiomethane (10 mmol) in THF (60 ml) under argon at -78 °C. The solution was stirred at this temperature for 1 h, and an appropriate alkyl halide (11 mmol) in THF (10 ml) was added. The mixture was stirred at -78 °C for 2 h, and warmed to room temperature overnight. The mixture was poured into saturated aqueous NH_4Cl (30 ml), and the aqueous layer extracted with Et_2O (3 × 30 ml). The combined organic layers were washed with H_2O (1 × 30 ml), dried over $MgSO_4$, and evaporated under reduced pressure to give the crude product, which was purified by column chromatography (silica gel, hexane/$CHCl_3$ = 2:1) to afford the pure products as pale yellow oils.

1-(Benzotriazol-1-yl)-4-phenyl-1-phenylthiobutane **7.4** ^{1}H-NMR δ: 8.01 (dd, 1H, J=1.1Hz and 8.1Hz), 7.63-7.58 (m, 1H), 7.43-7.00 (m, 12H), 6.14 (dd, 1H, J=6.4Hz and 9.0Hz), 2.68-2.34 (m, 4H), 1.82-1.68(m, 1H), and 1.60-1.47 (m, 1H). ^{13}C-NMR δ: 146.3, 140.8, 133.4, 131.3, 130.9, 128.8, 128.5, 128.2, 128.1, 126.9, 125.8, 123.8, 119.9, 110.8, 67.4, 34.6, 33.4, and 27.9. HRMS, *m/z* 360.1533 ($C_{22}H_{21}N_3S$ requires 360.1534).

Phenyl 3-(benzotriazol-1-yl)-3-phenylthiopropyl ether **7.6** ^{1}H-NMR δ: 8.01 (d, 1H, J=8.1Hz), 7.50 (d, 1H, J=8.3Hz), 7.41-7.30 (m, 2H), 7.28-7.16 (m, 3H), 7.14-7.07 (m, 4H), 6.97-6.78 (m, 3H), 6.42 (t, 1H, J=7.8Hz), 4.20-4.12 (m, 1H), 3.90-3.81 (m, 1H), and 3.00-2.82 (m, 2H). ^{13}C-NMR δ: 158.1, 146.1, 134.0, 131.9, 130.5, 129.3, 129.0, 128.9, 127.1, 124.0, 121.0, 120.0, 114.4, 110.5, 63.9, 63.6, and 34.0. HRMS, *m/z* 362.1330 ($C_{21}H_{19}N_3OS$ requires 362.1328).

1-(Benzotriazol-1-yl)-3-(naphth-1-yl)-1-phenylthiopropane **7.9** ^{1}H-NMR δ: 8.03 (d, 1H, J=8.1Hz), 7.84-7.68 (m, 3H), 7.52 (d, 1H, J=8.4Hz), 7.58-7.29 (m, 5H), 7.24-7.00 (m, 6H), 6.20-6.14 (m, 1H), and 3.20-2.74 (m, 4H). ^{13}C-NMR δ: 146.4, 135.4, 133.7, 133.6, 131.6, 131.3, 130.7, 128.9, 128.8, 128.7, 128.6, 127.2, 127.1, 126.8, 126.4, 126.0, 125.7, 125.5, 125.3, 124.0, 123.2, 120.1, 110.9, 66.9, 34.9, and 29.7. *Analysis* ($C_{25}H_{21}N_3S$): calcd: C 75.92 H 5.35 N 10.62. found: C 75.86 H 5.44 N 10.47.

2-[2-(Benzotriazol-1-yl)-2-phenylthioethyl]biphenyl **7.15** ^{1}H-NMR δ: 7.94-7.88 (m, 1H), 7.40-7.33 (m, 3H), 7.26-6.95 (m, 12H), 6.90-6.84 (m, 2H), 6.00 (t, J=8.0Hz), and 3.81 (d, 2H, J=8.0Hz). ^{13}C-NMR δ: 145.9, 141.9, 140.6, 133.3, 132.9, 131.5, 131.2, 130.1, 130.0, 128.7, 128.6, 128.4, 128.3, 127.3, 127.2, 127.1, 126.7, 123.5, 119.7, 110.2, 67.5, and 38.1. HRMS, *m/z* 408.1530 ($C_{26}H_{21}N_3S$ requires 408.1533).

4-(Benzotriazol-1-yl)-1-phenyl-4-phenylthiobut-1-ene **7.19** ^{1}H-NMR δ: 8.00 (d, 1H, J=8.3Hz), 7.65 (d, 1H, J=8.2Hz), 7.45-7.00 (m, 12H), 6.47-6.38 (m, 1H), 6.28-6.19 (m, 1H), 6.14-6.00 (m, 1H), and 3.41-3.22 (m, 2H). ^{13}C-NMR δ: 146.3, 134.1, 133.6, 131.6, 130.7, 128.9, 128.8, 128.7, 128.3, 127.5, 127.0, 126.1, 123.9, 123.1, 120.0, 110.8, 67.1, and 37.8. *Analysis* ($C_{22}H_{19}N_3S$): calcd: C 73.92 H 5.36 N 11.35. found: C 73.51 H 5.38 N 11.78.

1-(Benzotriazol-1-yl)-3-phenyl-1-phenylthiopropane **7.22** ^{1}H-NMR δ: 8.02 (d, 1H, J=8.1Hz), 7.54 (d, 1H, J=9.3Hz), 7.45-6.94 (m, 12H), 6.13-6.01 (m, 1H), and 2.90-2.57 (m, 4H). ^{13}C-NMR δ: 146.3, 139.2, 133.5, 131.5, 130.7, 128.8, 128.7, 128.6, 128.4, 128.3, 127.0, 126.2, 119.9, 110.7, 66.4, 35.5, and 32.3. *Analysis* ($C_{21}H_{19}N_3S$): calcd: C 73.01 H 5.54 N 12.16. found: C 72.78 H 5.56 N 12.55.

7.3.2 Cyclization of the Intermediate Products. General Procedure

Zinc chloride (10 mmol) was added to a solution of an appropriate alkylated product (5 mmol) in dry CH_2Cl_2 (20 ml) and the mixture refluxed for 12 h, cooled to room temperature, and poured into H_2O (20 ml). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 ml), and the combined organic layers washed with aqueous NaOH (1 N, 2 × 10 ml), water (2 × 10 ml), and dried ($MgSO_4$). Evaporation of the solvent gave the crude product which was purified by column chromatography (silica gel, hexane). Phenanthrene and naphthalene were compared to the respective authentic samples.

1-Phenylthio-1,2,3,4-tetrahydronaphthalene **7.3** Colorless oil. ^{1}H-NMR δ: 7.48-7.36 (m, 3H), 7.34-7.20 (m, 3H), 7.18-7.03 (m, 3H), 4.55 (t, 1H, J=3.9Hz), 2.87-2.66 (m, 2H), 2.29-2.14 (m, 1H), 2.08-1.88 (m, 2H), and 1.80-1.69 (m, 1H). ^{13}C-NMR δ: 137.5, 136.1, 135.4, 131.8, 130.5, 129.2, 128.9, 127.0, 126.9, 125.6, 47.6, 29.1, 28.4, and 18.6. HRMS, *m/z* 240.0969 ($C_{16}H_{16}S$ requires 240.0970).

4-Phenylthiochroman **7.7** Colorless oil. ^{1}H-NMR δ: 7.51-7.43 (m, 2H), 7.41-7.25 (m, 4H), 7.18-7.10 (m, 1H), 6.91-6.80 (m, 2H), 4.56-4.46 (m, 2H), 4.27-4.18 (m, 1H), 2.29-2.17 (m, 1H), and 2.05-1.96 (m, 1H). ^{13}C-NMR δ: 155.0, 134.8, 132.0, 130.9, 129.1, 128.9, 127.4, 120.7, 120.2, 117.0, 62.1, 42.8, and 27.6. HRMS, *m/z* 242.0769 ($C_{15}H_{14}OS$ requires 242.0765).

1-Phenylthio-2,3-dihydrophenalene **7.10** Light-yellow oil. ^{1}H-NMR δ: 7.76-7.64 (m, 2H), 7.49-7.18 (m, 9H), 4.81 (t, 1H, J=3.6Hz), 3.68-3.53 (m, 1H), 2.98-2.90 (m, 1H), and 2.30-2.11 (m, 2H). ^{13}C-NMR δ: 135.0, 134.6, 133.8, 133.7, 132.8, 129.0, 128.9, 127.7, 127.3, 126.0, 125.6, 125.5, 125.1, 124.4, 49.0, 27.2, and 26.1. *Analysis* ($C_{19}H_{16}S$): Calcd: C 82.57, H 5.83. found: C 82.72, H 5.92.

1-Phenylthioindan **7.23** Colorless oil. ^{1}H-NMR δ: 7.31-7.15 (m, 7H), 7.13-7.09 (m, 2H), 4.35 (t, 1H, J=6.8Hz), 2.91 (t, 2H, J=7.3Hz), and 2.19-2.10 (m, 2H). ^{13}C-NMR δ: 140.6, 134.0, 132.5, 128.8, 128.5, 128.4, 127.6, 126.1, 56.8, 37.0, 32.9. HRMS: *m/z* 227.0890 ($C_{15}H_{14}S$ requires 227.0894).

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Some commonly used additional notes are given below:

1. The list of reference is arranged in order of (a) year, (b) journal in alphabetical order of journal code, (c) part letter or number if relevant, (d) volume number if relevant, (e) page number.
2. In the reference list the code is followed by the complete literature citation in the conventional manner.
3. For journals which are published in separate parts, the part letter or number is given (when necessary) in parentheses immediately after the journal code letters.
4. Journal column numbers are not included in the code numbers unless more than one volume was published in the year in question, in which case the volume number is included in parentheses immediately after the journal code letters.
5. Patents are assigned appropriate three letter codes.
6. Frequently cited books are assigned codes, but the whole code is now prefixed by the letter "B-".

7. Less common journals and books are given the code "MI" for miscellaneous.

8. Where journals have changed names, the same code is used throughout.

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BIOGRAPHICAL SKETCH

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I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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